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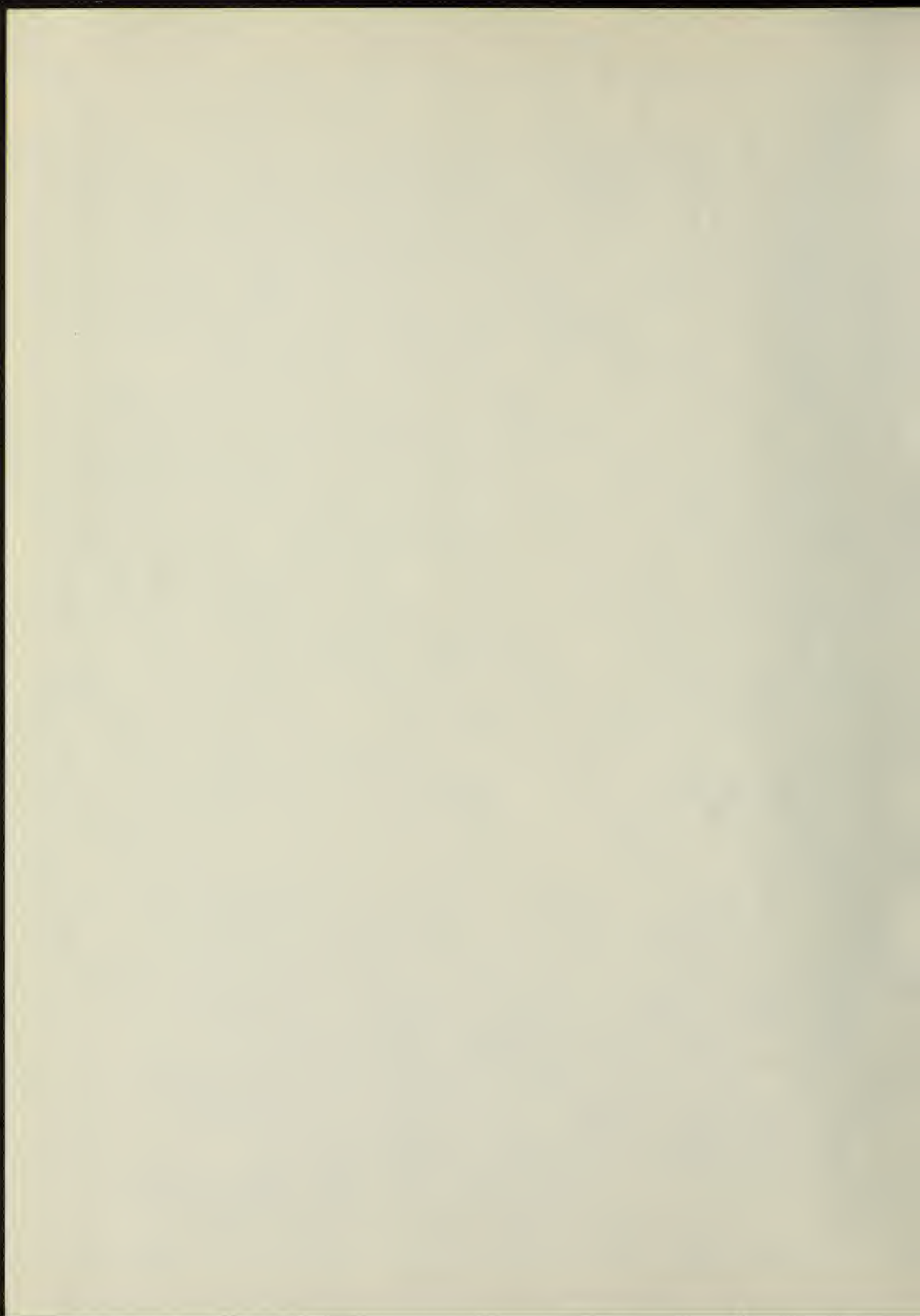
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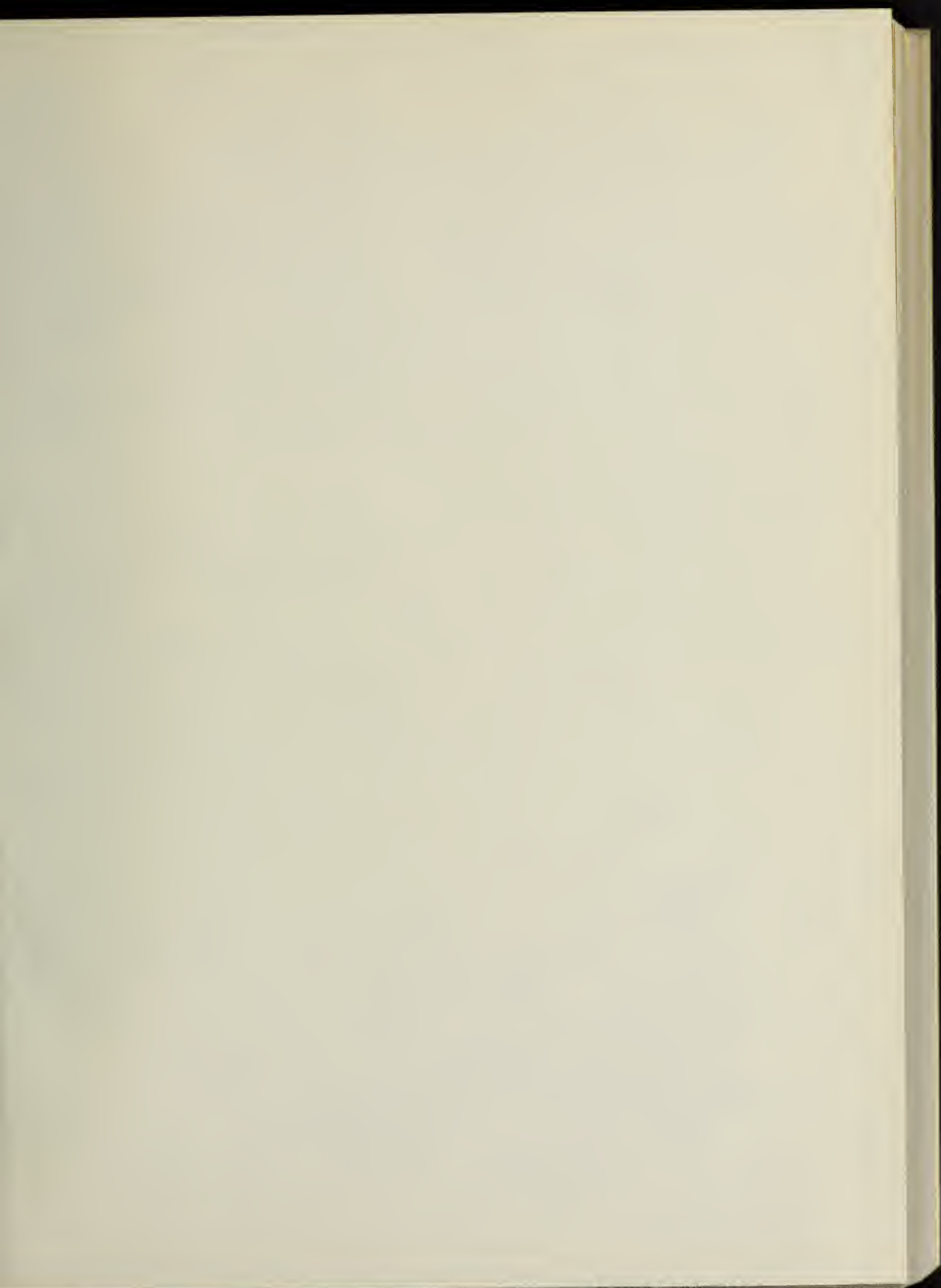
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NATIONAL CLEARINGHOUSE FOR MENTAL HEALTH INFORMATION

PSYCHOPHARMACOLOGY ABSTRACTS

Vol. 3 No. 7

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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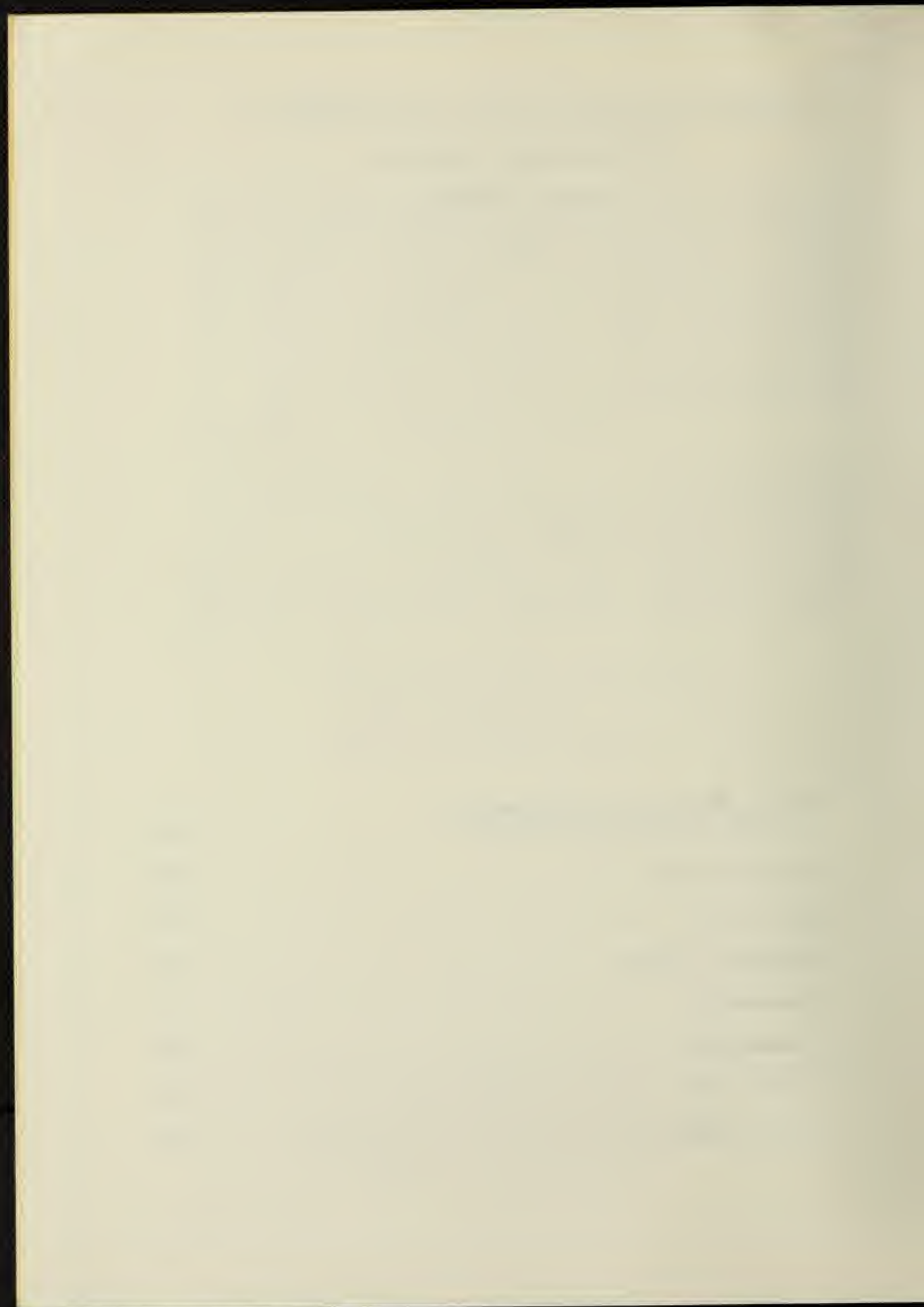
NATIONAL CLEARINGHOUSE FOR MENTAL HEALTH INFORMATION

PSYCHOPHARMACOLOGY ABSTRACTS

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REVIEWS, SUMMARIES, BIBLIOGRAPHIES, GENERAL ARTICLES AND BOOKS

1342 Third World Congress of Psychiatry. Proceedings of a symposium held at the Third World Congress of Psychiatry, Montreal, June 4-10, 1961. Rinkel, Max, ed. New York, Philosophical Library, 1963. 174 p. (Specific and non-specific factors in psychopharmacology.)

Ten essays are presented from a symposium on "Specific and Non-Specific Factors in Psychopharmacology" given at the Third World Congress of Psychiatry held in Montreal, Canada, in June 1961. The introduction states that in the unknown area of the relation of biochemistry to behavior, the interaction between the somatic and the symbolic necessitates a revision of premises, a recalibration of tools, and a reassessment of the rules; these essays examine the rules. The central problem of measurement in psychopharmacology is also of major concern. The subjects treated are: the specific effects of psychoactive drugs, a quantitative approach to psychopharmacology, test-score instability in measuring individual response, personality and drugs, variables and drug effectiveness, nondrug parameters of psychopharmacology, and individual animal variation in response to pentobarbital and dextroamphetamine. The pertinent literature is reviewed in each essay, and two formal discussions are included.

15 East 40th Street
New York, New York

1343 Thomas, E. Llewellyn. The psychopharmacology of analgesia. Applied Therapeutics, 5(10):857-864, 1963.

Recent findings in the mechanism of pain perception and analgesia indicate that the emotional and suggestive aspect thereof is of major importance, both in pain perception itself and the action of drugs that prevent it. Of the two types of nerve fibers transmitting pain signals (unmyelinated "C" fibers and myelinated Delta ("A") fibers), the C fibers are especially sensitive to depression by chemical means. Since these fibers mediate protopathic pain, which is the so-called "suffering" type and strongly emotional in origin, it is essential that at-

tention be paid in experiments with analgesia, not only to the drug used but also to suggestive and emotional factors inherent in the situation under study. Most clinicians agree that morphine remains the most powerful and valuable analgesic, although meperidine is now more popular. Methylnorphine is the most popular of the intermediate analgesics, and the salicylates remain the best of the minor analgesics. A table is given, listing the major, intermediate, and minor analgesics. Definite knowledge about the sites of action of analgesics is still lacking. For an analgesic drug to reach its full effect, anxiety must also be controlled.

Ontario Hospital
New Toronto, Canada

1344 Sourkes, Theodore L. Catecholamine metabolism and some functions of the nervous system. American Journal of Clinical Nutrition, 12:321-329, 1963.

A general discussion is presented of the naturally occurring catecholamines adrenaline, noradrenaline, and dopamine and their possible role in neurologic or mental illness. The biosynthesis of the catecholamines and the role of nutritional factors in this biosynthesis are given as preliminary discussions. Various theories on catecholamine level and catecholamine metabolism in relation to psychoses, psychoneuroses, and personality disorders are discussed. Theories have been constructed from the following questions: (1) Can human beings be characterized by their catecholamines? (2) Does the degree of change in catecholamine secretion bear any relation to the progress of treatment? (3) Are psychoses caused by an endogenous toxin resulting from defects in catecholamine metabolism? The functions of dopamine are discussed in detail. Variations in dopamine metabolism in normal subjects and inpatients with parkinsonism are described.

McGill University
Montreal, Quebec, Canada

- 1345 Remmer, H. & Merker, H. J. Drug-induced changes in the liver endoplasmic reticulum: Association with drug-metabolizing enzymes. *Science*, 142(3600): 1657-1658, 1963.

Administration of one or several i.p. injections of 50 to 100 mg phenobarbital/kg/day, or an alternate days, to normally fed rats, rabbits, and dogs produced certain striking changes in the endoplasmic reticulum of liver cells examined under the electron microscope. There is a marked increase in drug-metabolizing enzymes in the smooth membrane fraction. This increase was visible 48 hours after the first injection, reaching a maximum after the fifth injection. Livers of rabbits receiving one or two injections of 50 mg/kg phenobarbital showed increased activity of drug-oxidizing enzymes but no increase in quantity of smooth endoplasmic reticulum membranes or of procaine esterase activity. Besides phenobarbital, drugs with high lipid solubility, such as tolbutamide and nikethamide, produce liver changes. The result is to decrease the duration of action and effectiveness of a number of drugs metabolized to less effective or inactive compounds. Barbiturates, but not alkaloids, belong to the group of drugs producing these changes.

Freien Universität
Berlin-Dahlem, Germany

- 1346 Psychological effects of medication. *Medical Journal of Australia*, 1(1): 21-22, 1963.

It is difficult to assess correctly the psychological effects of medication. The doctor-patient relationship itself can modify such concrete things as secretion of gastric juices and height of blood pressure. The subject's personality is also a factor. Allowance must be made for error on the part of the observer. Even the method and manner of questioning a patient can have a modifying impact. Little is known as yet about the connection of suggestibility and the outcome of treatment. Finally, certain differences in personality behavior, habits, and education have been reported between placebo reactors and nonreactors, e.g., reactors receive greater relief of pain from morphine than do nonreactors.

(No address)

- 1347 Schou, Mogens. Normothymotics, "mood-normalizers". Are lithium and the imipramine drugs specific for affective disorders? *British Journal of Psychiatry*, 109(463):803-809, 1963.

Imipramine and a number of related drugs, amitriptyline, trimipramine, and N7001 are therapeutically active against depressive phases of the manic-depressive psychosis. They are effective in retarded as well as agitated depression. They have less stimulant action than do monoamine oxidase inhibitors and drugs related to amphetamine. They do not produce as much sedation as do the thioxanthenes. Lithium is therapeutically active against manic phases of the manic-depressive psychosis. Evidence is scanty as to the value of imipramine drugs in mania and lithium in depression. It is proposed that imipramine drugs and lithium should be placed in a new pharmacotherapeutic group to which the name normothymotics is given. The term should be restricted to drugs for which therapeutic or preventive activity (or both) against manic and depressive phases has been observed. It is characteristic of lithium and imipramine drugs that they do not influence the normal mind. They produce no apathy or impairment of consciousness or intellectual functions; they have no euphoriant or mood-depressant properties. Their therapeutic action on manic-depressives is similar to that of electric convulsive therapy (ECT), though they are supplemental to ECT rather than supplanters of it.

Institute of Psychiatry
Risskov, Denmark

- 1348 Nilsson, Eric. Origin and rationale of neurolept-analgesia. (Editorial) *Journal of Anesthesiology*, 24(3):267-268, 1963.

Phenoperidine and phentanyl have been found to produce complete general analgesia adequate for major surgical procedures. However, the respiratory depression caused by phenoperidine is intense, and both phenoperidine and phentanyl have marked emetic action. For use in anesthesia, therefore, these analgesics are best combined with neuroleptic agents with antiemetic properties, such as the butyrophenone derivatives haloperidol and dehydrobenzperidol. There are certain features of neurolept-analgesia that are marked: respiratory depression necessitating intubation of the trachea and positive-pressure ventilation; extremely stable circulation; and intense analgesia. A mixture of 60% nitrous oxide and 40% oxy-

gen can be given during neurolept-analgesia, and respiratory depression is reversed promptly at the operation's end by administering nalorphine in doses of 2 to 10 mg.

Lasarettet, Lund
Sweden

- 1349 Pender, John W. **Teratogenicity.** (Editorial) *Journal of Anesthesiology*, 24(3):650-657, 1963.

Results of the awareness of the teratogenic effect of thalidomide have taken the form of a reinvestigation of all drugs for unwanted teratogenic effects and the synthesis and investigation of new drugs for desired mutagenic effects. In animal experiments, a wide variety of agents (including acetylsalicylic acid, caffeine, thyroxine, vitamins, antibiotics, and the steroids) in certain dosages and under special circumstances, has produced malformation in one animal or another. Anesthetic agents cannot be dismissed as free of teratogenicity under all circumstances and must be re-examined as to teratogenic possibilities. Development of agents with desirable mutagenic effects may have to await further socio-philosophic development of man for acceptance of the concept of a "planned man."

(No address)

- 1350 Alper, Milton H., Flacke, Werner, & Krayner, Otto. **Pharmacology of reserpine and its implications for anesthesia.** *Journal of Anesthesiology*, 24(4):524-542, 1963.

The two major pharmacological actions of reserpine are these: (1) a behavioral effect (sedation); and (2) a slow decline of arterial blood pressure of moderate degree. Experiments conducted with reserpine on dogs, cats, rabbits, and mice are discussed as to: (1) actions on the CNS; and (2) cardiovascular actions. The influence of reserpine on the action of sympathomimetic amines is described, and the mode of action of sympathomimetic amines is tabulated. Pharmacological effects of reserpine in areas other than the nervous system are given, as are the drug's actions in man. Reserpine treatment and general anesthesia are discussed in regard to the drug's action on anesthetic potency and on circulatory response to anesthesia. Clinical reports are reviewed briefly. The main conclusion of this presentation is that patients on reserpine pre-

sent few problems that are fundamentally new and that would not be encountered in other patients. (186 references)

Harvard Medical School
Cambridge, Massachusetts

- 1351 Goldfien, Alan. **Pheochromocytoma: Diagnosis and anesthetic and surgical management.** *Journal of Anesthesiology*, 24(4):462-471, 1963.

Pheochromocytomas are functioning tumors arising in chromaffin tissue; epinephrine and norepinephrine are released by the tumor. These tumors should be considered as possible causes of hypertension, particularly when associated with hypermetabolism, glycosuria, weight loss, severe sweating, postural hypotension, or neurocutaneous syndromes. Prognosis depends upon establishment of the diagnosis, which can be confirmed or negated in the great majority by measurement of the catecholamines and their metabolites in plasma and urine. Preoperatively, serious pathologic disturbances can be controlled by oral doses of phentolamine. Anesthetic management has been handled successfully by the use of various anesthesia including nitrous oxide, ether, and epidural block in combination with muscle relaxants following thiopental induction.

University of California Medical Center
San Francisco, California

- 1352 Swerdlow, Mark. **The relief of pain after abdominal surgery.** *Anesthesia and Analgesia*, 42(5):588-595, 1963.

In the relief of postoperative pain, it is necessary to determine which drug to give, how much to give, and how to give it. Opiates are the most efficient pain relievers, but they often cause undesirable side effects, such as drowsiness, nausea, vomiting, and respiratory and circulatory depression. Postoperative analgesic agents should be ordered for the individual patient according to his needs and not in a routine pattern. They should always be administered intramuscularly. Opiates given when restlessness appears immediately in the postoperative period frequently causes a reversion to the anesthetized state and should, therefore, be deferred. A small dose of a phenothiazine agent i.v. is preferable. The dose of narcotic administered should be related to the patient's age, weight, general condition, and drug sensitivity. The optimum dose of

morphine for a healthy adult is 10 mg per 70 kg of body weight. After 48 hours, analgesic agents should be administered orally.

Salford Royal Hospital
Manchester, England

- 1353 Jensen, S. E. & Ramsay, Ronald.
Treatment of chronic alcoholism with lysergic acid diethylamide. Canadian Psychiatric Association Journal, 8(3):182-188, 1963.

Certain aspects of treatment with LSD-25 (lysergic acid diethylamide) given to alcoholics in Weyburn, Saskatchewan, are discussed through presentation of five case histories. Ages varied from 24 to 65 years, and all patients had a serious prognosis. Of 70 patients receiving the full program of treatment, 39 or 63% remained dry continuously following discharge as compared with only 27% who received group therapy only. The routine dosage was 200µg. The drug was administered at 9 A.M., and therapist remained with the patient throughout the day. There were three recognizable reactions to the LSD-25 treatment: the abreaction that occurred as the drug began to take effect; the transcendental experience, occurring from 1 to 4 hours after administration and only with doses over 100µg or 150µg; and the breaking down of defenses coupled with the inability to rationalize past and present behavior. It is not the effect of LSD-25 alone that is beneficial but the reaction brought about by the drug combined with a particular type of psychotherapeutic technique.

York County Mental Health Clinic
Newmarket, Ontario, Canada

- 1354 Modell, Walter. **Hazards of new drugs. The scientific approach is necessary for the safest and most effective use of new drugs.** Science, 139(3560):1180-1185, 1963.

The aim of all new therapies is the establishment of a more favorable ratio between probable adverse effect of treatment and probable adverse effect of untreated disease. To insure the safest and most effective use of drugs, preclinical testing, consideration of ecologic factors, sensitivities and resistances on the part of patients, ethical obligations, the lessening of outside pres-

ures, and the danger of too hasty publication of treatment results must all be taken into account.

Cornell University Medical College
New York, New York

- 1355 Wayne, George J. **Use of methohexital sodium in ECT.** Diseases of the Nervous System, 24(1):28-30, 1963.

The use of methohexital sodium as an i.v. anesthetic in EST is discussed. A 1% solution (500 mg methohexital in 50 cc of distilled water) was prepared. To anesthetize the patient, the dosage varied from 4 to 10 cc (40 to 100 mg). The average dose in the series reported was 70 mg. The solution was mixed with 1/75 gr of atropine for simultaneous administration. For injection, a 22-gauge needle was used, and the total amount was injected within 10 to 12 seconds. Anesthetization occurred within 30 seconds after injection and, with the needle in place, succinylcholine chloride was injected from a separate syringe. The optimal time for delivering the convulsive electrical impulse is between 45 and 60 seconds after this injection. A glissando technique was used in inducing the convulsion. The E and J Micro-daptor Respirator and a Guedel airway were used. A total of 1,276 treatments were given to 182 patients. Methohexital was found preferable to other barbiturates as premedication in EST because it promotes maximum comfort and freedom from anxiety, and enables the patient to regain alertness and self-sufficiency in the shortest possible time. The drug was proved of special value for elderly patients, 103 of those tested being between the ages of 53 and 76. However, if there is excessive psychomotor activity or intractable insomnia, thiopental or thiamylal is preferable to methohexital.

Edgemont Hospital
Los Angeles, California

- 1356 Lindsay, J. S. B. **Clinical trials in chronic schizophrenia.** (Letter) Medical Journal of Australia, 1(15):557-558, 1963.

In the paper by Dr. Horden and Dr. Somerville (The Medical Journal of Australia, January 12, 1963), which concluded that "a combination of trifluoperazine and tranlylcypromine was superior to placebo at the 5% level of significance," the data supplied by nurses were omitted on the grounds that nursing and occupational therapy tend

to lessen the effect of drugs. Dr. Lindsay contends that such data should never even be considered.

Malvern Clinic
321 Glenferrie Road
Malvern, Victoria, Australia

- 1357 Brody, J. A new look at enuresis. Medical Journal of Australia, 1(16): 578-580, 1963.

Enuresis is not a disease but a symptom. Nighttime control can be upset by excitement, disturbed sleep, dreams, nightmares, and overtiredness. There are also organic causes of bed wetting in children, including physical abnormalities, chronic cystitis, diabetes mellitus, and chronic nephritis. Investigation of the enuretic child must include chemical and microscopic examination of the urine, urine culture, and if indicated, radiological examination of the urogenital system. However, the largest group of enuretics fall into categories that are psychological rather than physiological. Consciously, they do not want to wet the bed, but subconsciously, they do. In treating the enuretic, therefore, it is necessary to discover and eradicate the emotional and psychological problems causing enuresis. In those cases where enuresis has become a habit beyond the cure of psychoanalytic eradication, waking drugs or sedatives, waking machines, and drugs, such as propantheline and imipramine, are helpful.

Gordonvale, Northern Queensland, Australia

- 1358 Judge, C. G. Problems of addiction. (Letter) Medical Journal of Australia, 1(16):599, 1963.

Comment is made on an article (Medical Journal of Australia, 1962, 1:317) on "Problems of Addiction." The author of this comment states that the solution to the difficult problem of drug dependence can be found by studies of the properties of the drugs themselves and their effects on patients. Certain drugs are more likely to produce dependency than are others, and this is not necessarily relative to their efficiency as tranquilizers and sedatives. There is also the possibility of the patient's having or being a drug-dependent personality, and this must be considered.

248 Drummond Street
Carlton, Victoria, Australia

- 1359 Rosanove, Ronald. Local anaesthesia for allergic patients: The use of diphenhydramine hydrochloride as a local anesthetic agent. Medical Journal of Australia, 1(17):613-614, 1963.

Certain antihistamine drugs provide practical alternatives for patients found allergic to the "caine" group of local anesthetics. Of antihistamines available, diphenhydramine hydrochloride (Benadryl) appears to be eminently suitable. In a 1% solution, diphenhydramine hydrochloride provided as effective an anesthesia as a 2% solution of procaine. The most common use by the author has been for local injection prior to taking skin biopsy specimens or the excision or electrodesiccation of achrochordons and other small localized benign skin lesions. No adverse reactions were observed in over 200 patients. Diphenhydramine hydrochloride also provided local anesthesia for relief of ulcerative stomatitis. The contents of one 50-mg capsule were dissolved in a teaspoonful of water and held in the mouth (usually 2 to 3 minutes), then swallowed.

Melbourne, Australia

- 1360 Swanton, Cedric. The dangerous amphetamines. (Letter) Medical Journal of Australia, 1(21):795, 1963.

Amphetamine drugs and their derivatives can become the basis of most intractable addiction. This is because amphetamine is so easily procurable, gives the individual a sense of well-being, and at least initially, the subject is not aware that addiction is occurring. Amphetamine can cause sexual excitation and immoral behavior, and can produce a condition indistinguishable from paranoid schizophrenia. The place of amphetamine in medical treatment is questionable, as its value does not appear to transcend that of other drugs less conducive to addiction.

B. M. A. House
135 Macquarie Street
Sydney, Australia

- 1361 Wilkins, G. D., Lea, R. V., Nicholson, A. L., Oldmeadow, D. J., & Richards, W. R. A therapeutic community development in a state psychiatric hospital. Medical Journal of Australia, 2(6):220-224, 1963.

A unit was established for patients of both sexes, the majority being between 16 and 40 years of age, of average or better intelli-

gence, able to sustain a full day's activity, and minimally subject to dependence on drugs, including alcohol. Physical treatment is minimum, consisting of the use of barbiturates, tranquilizers, and antidepressant drugs. Individual and group psychotherapy (counseling and analysis), work, social and educational activities, and community government constitute the features of the therapeutic program. Results have proved that such a therapeutic community can only benefit the psychiatrically disturbed patient. During the first 3 years of the operation, 310 patients passed through the unit, 221 being discharged within 12 weeks and another 33 by the end of the 16th week, with the remainder spending periods of up to 68 weeks.

Larundel Hospital
Bundoora, Victoria, Australia

- 1362** Bridges-Webb, C. **Anaesthetics in general practice: A review of 300 administrations.** Medical Journal of Australia, 2(8):347-353, 1963.

Results are presented of a survey that was made to assess the range of surgery; types of patients; and the suitability, results, and complications of anesthetics given in one country general practice. Children under 10 years of age comprised 29% of the patients, those from 10 to 19 years of age comprised 15%, elderly patients over 60 years of age accounted for 4%, but the majority (52%) were from 20 to 59 years of age. Female patients predominated, but complications were more common in males. Nearly one-third of the anesthetics were for emergency surgery; less than one-fifth of the surgery was of a major nature, and most of the anesthetics were for short duration. Pethidine was found to be very suitable for routine use as premedication. An increased incidence of complications associated with open-ether anesthesia in children was noted. Vomiting and obstruction of the airway were the most common complications in all the patients. Postanesthetic complications were not common.

Traralgon, Victoria, Australia

- 1363** Shaw, F. H. **Barbiturate intoxication.** (Letter) Medical Journal of Australia, 2(13):557-558, 1963.

False claims and maladministration are blamed for failures of Lemegrade as a safe drug. Bemegrade actually is considered the most

reliable of analeptics. It has been observed to bring about a tangible stimulation of respiration and a simultaneous hyperreflexia in gravely poisoned patients. As a central analeptic, bemegrade does not cause hypertension and overtaking of the already intoxicated myocardium nor does it cause hyperpyrexia. Various mixtures of barbiturates with bemegrade are available for the treatment of drug overdosage. More attention should be given to drugs other than barbiturates for producing sleep. Monoureides, such as carbromal and bromvaletone, should be used more often; they are safe and nonaddictive.

University of Melbourne
Parkville, Victoria, Australia

- 1364** Yeates, R. H. **Anaesthetics in general practice.** (Letter) Medical Journal of Australia, 2(13):558, 1963.

In a well-administered ether anesthetic, vomiting should rarely occur, and oxygen is rarely necessary. Ethyl chloride should not be given to a child under 5 or 6, nor to the elderly. It is not so much the type of anesthetic that is so important, but rather the skill of the anesthetist in its administration.

High Street
Boonak, Ohio

- 1365** **Amphetamines.** British Medical Journal, 1(5324):173, 1963.

Amphetamines and tranlycypromine potentiate the effects of adrenaline and other sympathomimetic amines; combinations may cause hypertensive effects in severity, ranging from trivial to fatal. A recent clinical trial of 10 mg dexamphetamine in the treatment of depression showed it to be no more beneficial than placebo. Dexamphetamine combined with cyclobarbitone is more euphoriant than either drug alone. Tranlycypromine has some therapeutic effects on depression in 30 to 150 mg/day doses.

(No address)

- 1366** Bell, D. S. **The dangerous amphetamines.** (Letter) Medical Journal of Australia, 2(6):251, 1963.

Amphetamines have a pernicious, addictive affect on users. Addiction to phenmetrazine and diethylpropion, as well as to methyl-

phenidate and pipradol and less well-known preparations taken in substitution for amphetamine, has also been widely documented. These other stimulants should be included in any restrictions set up for the amphetamines.

Callan Park Hospital
New South Wales, Australia

- 1367 Ellard, John. **Psychotropic drugs in general practice.** Medical Journal of Australia, 2(19):773-777, 1963.

The use of pharmacological agents in psychiatry needs to be reassessed. The primarily sedative chemical remedies used are phenothiazines, barbiturates, chlorthalidoxime, and meprobamate; the primarily antidepressants are sympathomimetic amines, MAO inhibitors, imipramine, and amitriptyline. The phenothiazines produce certain side effects, but are none the less remarkably safe. They are particularly indicated in the treatment of psychotic excitement and agitation, whatever the cause. There is no evidence to suggest that phenothiazines are superior or even equal to a skillfully used barbiturate in the usual neurotic anxieties. For a depression of moderate degree not helped by a simple preparation, either amitriptyline or imipramine should be used. For severe depression, a psychiatrist should be consulted. Electroconvulsive therapy is still the most effective and safest treatment.

Sydney, Australia

- 1368 **Cyclizine.** Medical Journal of Australia, 1(14):529-530, 1963.

Cyclizine is used as an antiemetic and a remedy for motion sickness. After hundreds of millions of doses, there is no clinical evidence of damage to or abnormal development of the human fetus. Laboratory experiments on animals indicate that at a very high dose level there is some abnormal fetal development. The average woman who takes cyclizine during pregnancy would weigh between 50 and 60 kg. If she takes 50 mg of the drug t.i.d. (before meals), she is taking approximately 1/50th the dose given the experimental rabbits. This laboratory experiment would not prove that cyclizine is a teratogenic compound in humans.

(No address)

- 1369 Currie, T. T. & Cole, W. H. J. **Methoxyfluorane.** (Letter) Medical Journal of Australia, 1(14):524, 1963.

Safe procedures for the use of the inflammable anesthetic ethylene are highly described. The addition of 1% or 2% methoxyfluorane to ethylene with 20% oxygen prevents the rise of ethylene to electrical switches and eliminates ignition hazard because of the higher molecular weight of methoxyfluorane, which gives a final density exceeding air. Many anesthetic mixtures of ethylene are noninflammable, such as cyclopropane 10%: ethylene 70%: oxygen 20%, and cyclopropane 10%: ethylene 60%: hydrogen 10%: oxygen 20%.

East Melbourne, Australia

- 1370 Inglis, W. **An elegant phrase.** (Letter) Medical Journal of Australia, 1(14):524, 1963.

"Insidon" is classed as a "psycho-autonomic harmonizer" because it assists in restoring normal function of mind and body in patients through its mood-elevating and tranquilizing actions.

St. Leonards
New South Wales, Australia

- 1371 Ibister, Clair. **Poisoning in childhood, with particular reference to kerosene poisoning.** Medical Journal of Australia, 2(16):652-656, 1963.

In a general discussion on accidental poisoning in childhood, three main aspects are discussed: (1) the general pattern of hospital admissions, including the incidence of poisoning reported from the most common toxic agents; (2) the pattern of the most frequent cause of poisoning and death—kerosene; and (3) lessons derived from accumulated data, which suggests certain preventive measures. Case histories from the main children's hospitals in four Australian states, compiled from 1958 to 1962, involving 3,196 children (28 deaths) were examined. Results are discussed of a series of 348 cases of kerosene poisoning and 72 cases of fly-spray ingestion studied from the points of view of age, sex, treatment, complications, and hospital stay. The following conclusions were reached for the treatment of kerosene poisoning and ingestion of fly-spray without halogenated hydrocarbons or organic phosphates: (1) No effort should be made to induce emesis. (2) Gastric lavage

should not be done. (3) Fresh or evaporated milk should be given. (4) If there is evidence of pulmonary edema, steroids and the positive-pressure machine may save life. (5) Penicillin is indicated if there has been moderate to severe coughing.

Royal North Shore Hospital
Sydney, Australia

1372 Thorp, R. H. Some observations on the toxicology of common household poisons of importance in paediatrics. Medical Journal of Australia, 2(16):658-659, 1963.

The most important household substances responsible for poisoning in infants and children are the petroleum distillates and pesticides containing strychnine. The aromatic impurities that give kerosene its objectionable odor are the cause of its toxicity. The purification of kerosene and all petroleum distillates would considerably lessen their dangers. The worst treatment is to induce vomiting; the best is to give milk. Kerosene harms only when it enters the lungs and so it is essential to retain ingested kerosene in the stomach.

University of Sydney
Sydney, Australia

1373 Johnson, Alex. The commonwealth poisons register. Medical Journal of Australia, 2(16):659-660, 1963.

The preparation of a register of poisonous substances, which will contain information on toxicity and treatment, is described. Each poisonous produce is to be listed separately on a file card. The master set of cards is to be kept at Canberra, and one or more sets will be sent to each State Health Department. A manual on poisons will be compiled; copies will be available for distribution to each state, and one will be kept at every poison-control center. The last link in the poison-control scheme will be an Information Bulletin.

Commonwealth Department of Health
Canberra, Australia

1374 Currie, Trevor T. Anesthetics in general practice. (Letter) Medical Journal of Australia, 2(18):762, 1963.

The author of this letter states that a transition is occurring in the practice of anesthesia in Australia. The transition is

away from the outdated open-ether technique and toward better alternatives. Although ether is safe, it produces nausea and vomiting in 50% of the cases. Most patients who have had ether ask for an alternative the next time. A general practitioner can achieve a controlled but expanding degree of anesthetic proficiency by choosing from the whole range of anesthetic methods currently available. It is towards this range that undergraduate anesthetic education should continue to progress, along with the abolition of the limited practice of an obsolete technique such as open ether.

132 Grey Street
East Melbourne, Australia

1375 Lomaz, J. G. Anesthetics in general practice. (Letter) Medical Journal of Australia, 2(22):936, 1963.

The author criticizes the abolition of the open-ether method of anesthesia in general practice, as was advocated in the November 2, 1963 issue. He states that the open ether technique is necessary with children—many have to be anesthetized in isolated circumstances and for a variety of procedures. Ether is simple to administer and, when given with oxygen, it is safe. In this context, it should be continued to be taught to undergraduate students and resident general practitioners until the services of trained anesthesiologists are available to a larger number of patients.

22 Peel Street
Kirribilli, New South Wales, Australia

1376 Lawrence, W. Anesthetics in general practice. (Letter) Medical Journal of Australia, 2(26):1061, 1963.

A brief comment on the desirability of using the open-ether method of anesthesia in general practice is given. The author states that open ether is a must for both the specialist and the general practitioner. It is easily administered, is safe, is a muscle relaxant, and has a few toxic or side effects. Open ether is especially indicated for children. This method of anesthesia should not be dropped from the training of undergraduates.

5 Goulbourn Avenue
Redcliffs, Victoria, Australia

- 1377 McBride, W. G. **The teratogenic action of drugs.** Medical Journal of Australia, 2(17):689-693, 1963.

To ascertain the dangers of various drugs taken during pregnancy, a study has been made of the abnormalities in babies born at The Women's Hospital in Sydney, Australia, in the 5-year period from 1957 to 1962. The first part of the study is devoted to thalidomide. Of 404 severely malformed babies born over this period, 14 had typical abnormalities caused by this drug. The stage of pregnancy at which the women took thalidomide and gave birth to an affected infant, the abnormalities, and whether the baby lived or died are tabulated. (Of 17 affected babies, 10 died.) The stage of pregnancy at which women took thalidomide and gave birth to a normal infant is also tabulated. The types of malformations present in the remaining 387 babies are categorized. Seventy-five of the mothers took no drugs. The various drugs ingested by the patients were ferrous compounds alone, 49; cyclizine HCl, 24; phenmetrazine, alone or in combination, 41; acetazolamide, alone or in combination, 40; chlorothiazide, alone or in combination, 56; and trifluoperazine, 1. A brief discussion is given of these drugs and the progestogens. In this study, thalidomide is the only drug that can be accused of causing congenital anomalies. Pregnant women should be given as few drugs as possible, and these drugs, in reasonable doses, should first be proved nonteratogenic to New Zealand white rabbits and rats.

Sydney, Australia

- 1378 **Meclozine hydrochloride removed from commonwealth pharmaceutical benefits list.** Medical Journal of Australia, 1(3): 100, 1963.

The drug meclizine hydrochloride, used to treat allergies, motion sickness, and nausea in pregnancy, was removed from the Commonwealth pharmaceutical benefits list (Australia) as of January 1, 1963, because a Swedish doctor suspected that it might be responsible for deformities in infants whose mothers had taken it during early pregnancy. Although the suspicions reported in Sweden had not been confirmed in Australia, the drug was removed until further information was available. It was recommended that medical practitioners, in the meantime, use special care in prescribing the drug.

(No address)

- 1379 Horton, Robert H. **Methoxyfluorane.** Medical Journal of Australia, 1(11): 409-410, 1963.

Because of a report in the December 29, 1962 issue on the use of ethylene and methoxyfluorane as anesthetics, the present author, a member of the Standards Association of Australia Subcommittee, states that difficulties will be introduced if ethylene is reestablished as an anesthetic. Present operating theaters would be unsafe, and the problems in providing safe conditions would be great. Many major alterations would be needed in the operating theater itself. The committee does not want to dictate to the medical profession, but it does want to make the dangers of ethylene known.

Alfred Hospital
Prahran, Victoria, Australia

- 1380 Clements, F. W., Southby, Robert, Rowlands, J. B., & Veuthey, P. **An analysis of deaths from accidental poisonings in children aged under five years.** Medical Journal of Australia, 2(15):649-652, 1963.

A survey was made in four Australian states of coroners' depositions of children under 5 years of age who died from the effects of acute poisoning between 1955 and 1961. Information was sought on the nature of the poisonous substance and its accessibility, the time intervals between ingestion, and recognition and appropriate action taken by adults. The causes of death were: petroleum distillates (kerosene) in 47 children; drugs (strychnine, barbiturates, aspirin, ferrous sulfate, laxatives, chlorpromazine, liniments, and imipramine) in 62; animal poisons, pesticides, and insecticides in 38; and household and workshop substances in 20. The death rate was significantly lower in Victoria than in the other States and may, in part, have been the outcome of an intensive educational campaign over the previous few years. Queensland and Western Australia had higher death rates than New South Wales. In each State, a higher percentage of deaths occurred in the country compared with the metropolitan areas than might have been expected from the distribution of populations. Kerosene claimed the largest number of victims, followed by strychnine, insecticides, and animal poisons. The significance of some aspects of labeling and marketing of a number of substances, including power kerosene and quinine, ergot, and strychnine tablets, is discussed. It is suggested that death rates from acute poisoning in this age

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group could be greatly reduced by certain legal action and by better educational campaigns.

University of Sydney
Sydney, Australia

CLINICAL STUDIES

1381 Browne, M. W., Kreeger, L. C., & Kazamias, N. G. **A clinical trial of amitriptyline in depressive patients.** *British Journal of Psychiatry*, 109(462):692-694, 1963.

Seventy depressed patients, 45 endogenous and 25 reactive, were included in a double-blind controlled trial to assess the value of the use of amitriptyline in such cases. Tablets that were identical in appearance to the real drug were used as placebo; the chief pharmacist was the only person who knew which patients were receiving the real drug and which the placebo. At the beginning of treatment, the patient's symptoms were noted and scored on a chart as to the following: depression, guilt, suicidal ideas, agitation, retardation, anxiety, feelings of paranoia or depersonalization, obsessional symptoms, hypochondriasis, appetite, weight loss, and insomnia. The patients were seen at weekly intervals over a 4-week period, and the above symptoms were reassessed as to improvement or lack of improvement. Taking both reactive and endogenous depressions together as a group, 35 patients received the drug, and of these, 22 were improved by treatment. Thirty-five patients received the placebo, and of these, 11 were improved by treatment. The two main side effects complained of were trembling of the hands and tiredness. One patient became hypomanic, but this subsided when the drug was withdrawn and chlorpromazine substituted. A favorable result to a statistically significant degree was seen in reactive depression. In endogenous depression, the results were in favor of the drug over placebo, but were not of statistical significance.

Fairdene and Netherne Hospitals
Coulson, Surrey, England

1382 Master, Roshen S. **Amitriptyline in depressive states. A controlled trial in India.** *British Journal of Psychiatry*, 109(463):826-829, 1963.

Hamilton's Rating Scale for Depression, which provides both target symptoms and a generally accepted rating scale, was used

to evaluate the effects of amitriptyline in the treatment of depression in outpatients. Of 61 patients who started the trial, only 12 completed the full 12-week study. Ratings were done at the end of 3, 6, 9, and 12 weeks. Dosage was 25 mg amitriptyline or placebo t.i.d. for the first week, followed by 50 mg t.i.d. for the subsequent weeks. The overall improvement from amitriptyline was significantly higher than that from placebo for the first 3 weeks, but subsequent improvements were not significant. Side effects were generally not severe; dry mouth and constipation were most frequently complained of. Hallucinatory excitation was produced in two patients with schizophrenia, and they were immediately withdrawn from the trial. Nine of the 12 patients who completed the trial (10 on the drug, 2 on placebo) and who were receiving active drug remained symptom free for 5 months following drug withdrawal.

Directorate of Social Welfare
Maharashtra State, Poona, India

1383 Milner, G. **Ascorbic acid in chronic psychiatric patients—A controlled trial.** *British Journal of Psychiatry*, 109(459):294-299, 1963.

A controlled, double-blind trial of ascorbic acid saturation, involving 40 male, chronic psychiatric patients, is described. Their mean age was 52.6 years (range, 29 to 69 years), and their mean length of hospitalization was 17.7 years (range, 3 to 45 years). Four patients were suffering with manic depressive psychosis, two with G.P.I., and 34 with schizophrenia. The 20 patients in the active group received 1 g of ascorbic acid solution per day; the other group received an inert solution. Both the M.M.P.I. and the W.P.R.S. rating scales were used to assess any psychological changes in the patients. Physical examination and Hb percentage showed that none of the patients were markedly anemic, and there were no significant changes in Hb percentage. The results with the M.M.P.I. scale showed significant improvement at the 1% level of prob-

ability in the active group. The W.P.R.S. scale rating for the active and placebo groups is given in tabular form and shows more improvement in the active group than in the placebo group. Subjective feelings of improvement in general well-being were reported by eight patients, five of these being in the active group. Statistically significant improvement in the depressive, manic, and paranoid symptom complexes, together with an improvement in overall personality functioning, was obtained following saturations with ascorbic acid.

Towers Hospital
Leicester, England

- 1384 Oltman, Jane E. & Friedman, Samuel. **Comparison of temporal factors in depressive psychoses treated by EST and antidepressant drugs.** American Journal of Psychiatry, 119:579-580, 1963.

A statistical comparison is made of EST-treated depressions (1952 to 1955) and antidepressant drug-treated depressions (1959 to 1960) during a 2-year period following admission to hospital. The study was made on 191 females with depressive psychosis. Statistical figures indicate that length of hospitalization was definitely shorter in the drug period than in the EST period. In the EST period, 60% of the patients were hospitalized for more than 3 months, as compared with 31% in the drug period. The average length of total hospitalization during the drug era was only 37% of that observed during the EST period. A summary of the patients' status at the end of 2 years of followup reveals that 20% of the EST group were still hospitalized, as compared with only 6% of the drug-treated group. Mortality rate was approximately the same for both groups. One patient in the drug-treated group committed suicide. With respect to readmissions, there appears to be a slight advantage in favor of the EST group. It may be conservatively concluded that the duration of hospitalization in female patients with depressive psychosis has not been lengthened during the current era of antidepressant-drug therapy.

(No address)

- 1385 Orbell, Geoffrey. **Headaches and migraine associated with eyestrain. Preliminary report of a trial of chloridazepoxide.** British Journal of Ophthalmology, 47:246-247, 1963.

In a 4-month preliminary study, thirty-six patients with headaches and migraine associated with eye strain, 9 males and 25 females from 13 to 63 years of age, showed excellent improvement on chlordiazepoxide. Twenty-nine of the patients had either exophoria or esophoria of varying degrees of severity; the other seven suffered from typical ophthalmoplegic migraine. The drug dosage varied from 10 to 30 mg daily. All 36 patients lost their symptoms after a few days. In some patients, headaches returned in 4 to 6 days after termination of dosage. No side effects appeared at this rather low dosage.

Invercargill, New Zealand

- 1386 Rao, M. N., Cale, J. O., & Jenkins, M. T. **The antiemetic efficacy of fluphenazine with comparative results of the inventory and biometrical evaluation.** Anesthesia and Analgesia, 42(2):253-261, 1963.

A double-blind study on 205 patients was conducted to determine the effectiveness of fluphenazine as an antiemetic. Sixty-seven patients received a blank; 24 of these were nauseated or vomited in the postanesthetic period. Seventy-nine patients received 5 mg of fluphenazine i.m., 30 to 45 minutes before the termination of surgery; 7 of these were nauseated or vomited during the postanesthetic course. Of the 32 patients who received 2.5 mg of fluphenazine i.v., 3 displayed continuing nausea and vomiting. The results were subjected to two forms of biometrical analysis---the RI-DIT system and multiple regression. It was found that the drug, when given i.m., in this dosage at the stated time interval before the end of the surgical procedure, afforded protection against postoperative emesis, whereas i.v. fluphenazine aided in the treatment of such symptoms once they appeared and caused no untoward side effects. Considering the efficacy of the fluphenazine administered i.v. when nausea, retching, or vomiting occurred in the postoperative period, as well as the minimal occurrence of side effects, it is felt that this is the preferable method of approaching the treatment.

Parkland Memorial Hospital
Dallas, Texas

- 1387 Rawlings, W. U., Ferguson, R., & Madison, T. G. **Phenmetrazine and trifluoperazine.** (Letter) Medical Journal of Australia, 1(10):370, 1963.

In refutation of a warning note that reported teratogenic effects from trifluoperazine, data are presented from 341 pregnancies in abortion-prone patients treated with trifluoperazine, in which the incidence of congenital abnormalities (1.46%) was no higher than that in the general population (1.5%). Duration of trifluoperazine treatment was from first examination in pregnancy until emotional stability was assured.

The Royal Women's Hospital
Carlton, Victoria, Australia

- 1388 Dukes, D. C., Blainey, J. D., Cumming, G., & Widdowson, G. **Treatment of severe aspirin poisoning.** Lancet, 2: 329-331, 1963.

The removal of salicylate by hemodialysis and simultaneous forced diuresis was measured in six patients with acute aspirin poisoning, and was compared with the effects of forced alkaline diuresis in five patients with poisoning of the same severity. In all 11 patients, some form of salicylate had been taken in amounts varying from 26 to 98 g, between 3 and 14 hours before admission. All patients recovered rapidly, but the hemodialysis method was the more efficient method. In each case, clinical improvement was related to reduction in serum-salicylate level. If an artificial kidney is not available, forced alkaline diuresis should be used. A method for treating acute aspirin poisoning by forced alkaline diuresis is described.

The General Hospital
Birmingham, England

- 1389 Stapleton, Thomas. **Sleep-walking as a manifestation of anxiety due to mourning.** Medical Journal of Australia, 1(13):470-474, 1963.

The case of a boy, 8 years of age, who was sleepwalking due to anxiety over losing a close uncle is reported, in order to draw attention to the possible effects of suppressing mourning and the dangerous potential of tranquilizers in fixing a basic causative factor in an anxiety state. The family doctor had treated the boy with tran-

quilizers, which for 6 weeks led to less disturbance at night, but the improvement was not sustained. Fortunately, the tranquilizers that were prescribed by the practitioner were not given in a large enough dose to stop the sleepwalking and the sleepwalking completely. Had this occurred, the disturbance might have been fixed in the child for life, and it might have emerged in a different way some years later. It is not wise to get out of the difficulty posed by inadequate training by prescribing tranquilizers. If tranquilizers are used, they must not be allowed to mask the psychopathology of a patient.

University of Sydney
Sydney, Australia

- 1390 Currie, T. T. & Cole, W. H. J. **Methoxyfluorane—a report of 300 cases of clinical anaesthesia.** (Letter) Medical Journal of Australia, 1(5):172, 1963.

In an extension of previously reported work on methoxyfluorane, the use of this anesthetic combined with ethylene and oxygen is briefly reported. This combination alleviates the coughing, hypotension, and prolonged recovery time associated with the usual methoxyfluorane--nitrous oxide--oxygen combination. The inflammability of the mixture was not tested.

Melbourne, Australia

- 1391 Pitt, Aubrey & Goble, A. J. **Clinical evaluation of "Tersavid", "Marplan" and "Segontin" in angina pectoris.** Medical Journal of Australia, 1(13):466-468, 1963.

Double-blind controlled trials of "Tersavid" (RO 4/1364), isocarboxazid, and prenylamine were carried out on patients with angina pectoris. Eleven patients were admitted to the RO 4/1364 trial and were given a dosage of 100 mg t.i.d. Five females and four males, ranging in age from 42 to 66 years, completed this trial. Ten patients were given 10 mg of isocarboxazid q.i.d. The four females and five males who completed the isocarboxazid trial ranged in age from 46 to 67 years. Eight patients, four females and four males, ranging in age from 43 to 68 years, received 30 mg of prenylamine t.i.d. in this trial. It was found

that the three drugs, in the dosages used, were no more effective than placebo tablets. No adverse effects attributable to the drugs were observed.

Royal Melbourne Hospital
Melbourne, Australia

- 1392 Bortoluzzi, E., Roella, C., Bortoluzzi, S. Longoni, & Montoli E.
Methylphenidate in the treatment of shivering. *Anesthesia and Analgesia*, 42(3):325-331, 1963.

This study was conducted to determine the mode of action and the effectiveness of methylphenidate in the treatment of shivering observed in 95 patients. The causes of shivering were spontaneous loss of heat, sepsis, and intravenous blood and fluid administration. Methylphenidate was administered i.v. in doses ranging from 20 to 60 mg. Shivering ceased very rapidly in 90.5% of the patients, and this was followed by an improvement in circulation, respiration, and general well being. In some instances, the general body reactions to temperature change were unaffected even though shivering ceased, indicating that the drug does not have an antipyretic effect. It is postulated that, being structurally similar to the diphenylmethane group of drugs, methylphenidate acts upon the reticular substance of the brain stem.

Ospedale di Circolo
Varese, Lombardia, Italy

- 1393 Rail, L. **Treatment of infantile spasms with ACTH.** *Medical Journal of Australia*, 2(17):708-709, 1963.

Results are given of the treatment with ACTH of 34 subjects in a series of 44 cases of infantile spasms. Infantile spasms are a form of epilepsy occurring the first year of life and displaying a characteristic EEG pattern (hypsarrhythmia). Clinical features of the disorder are discussed, and the cases that are most likely to respond to treatment are described. Doses of ACTH ranged between 10 and 50 units/day; if no change in EEG occurred in 7 days, initial doses of 25 units/day were raised to 50 units/day. Of the 34 ACTH-treated patients, 6 showed marked improvement and 16 showed some improvement. Of the 10 untreated patients, only 1 improved when the spasms ceased

spontaneously. The ACTH had a remarkable effect on the encephalopathic state seen in infantile spasms; the mechanism of action is not known.

Sydney, Australia

- 1394 Misès, R. & Beauchesne, H. **Essai du carbamate de phenyl-éthynyl-carbinol en psychiatrie infantile.** (Trial of alpha-ethynylbenzyl carbamate in child psychiatry.) *Revue de Neuropsychiatrie Infantile et d'Hygiène Mentale de l'Enfance*, 11:675-678, 1963.

A trial of α -ethynylbenzyl carbamate was conducted in 49 children and adolescents. Dosage began with 1/2 tablet (0.15 g), and if improvement was noted, this was increased by 1/2 tablet/day to an average of 3 tablets/day for the younger children and 5 tablets/day for adolescents. Results were very satisfactory (VS), satisfactory (S), moderate (M), or unchanged (U), as indicated, in the following diagnostic groups: anxiety and neurosis (VS) 7, (S) 3, (M) 1, (U) 2; character disturbance (VS) 5, (S) 2, (M) 1, (U) 1; self mutilation (U) 4; and epilepsy (VS) 6, (S) 5, (M) 1, (U) 1. The self-mutilation patients had been receiving fairly large doses of levomepromazine, and α -ethynylbenzyl carbamate was substituted gradually at the rate of one tablet of 0.30 g α -ethynylbenzyl carbamate for each tablet of 0.25 g levomepromazine. The α -ethynylbenzyl carbamate had no effect on epileptic seizures. Nausea and vomiting occurred in a few cases, necessitating interruption of treatment in one patient. The sedative action of the drug was not accompanied by hypnotic effect. The effect of α -ethynylbenzyl carbamate on individual components of the above disorders are discussed briefly.

(No address)

- 1395 Macris, Spyros G., Macris, Gerasimos J., Cacouri, Alexandra N., & Karapiperis, Spyros N. **Intravenous methylphenidate for the treatment of singultus.** *Anesthesia and Analgesia*, 42(4):440-442, 1963.

Because of previous favorable results from the use of methylphenidate in treating singultus (hiccups) in a limited number of cases, a more extensive trial was made. During an 18-month period, 20 mg of the drug were given i.v. (within 30 seconds) a total of 96 times to 58 patients (57 males and 1

female, 15 to 86 years old). The singultus had occurred in 3 patients at the induction of anesthesia and in 30 patients postoperatively; in 27 patients, it was unrelated to the operation. (A table gives the probable causes in more detail.) A placebo was injected i.v. to a control group of 15 patients who were also suffering from singultus. Singultus stopped in 93 of the cases but recurred in 55, between 15 minutes and 24 hours after cessation (average, 175 minutes). The singultus stopped with only four of the placebo patients. No side effects were noted with the drug. No explanation of the mode of action of methylphenidate can be offered. A scheme of administration should be developed for cases where a sustained effect is desired.

Army Pension Hospital
Athens, Greece

1396 Tamir, A. & Braham, J. L'influence de l'A.C.T.H. sur les tracés électro-encéphalographiques d'enfants atteints de phenylketonurie. (Effect of ACTH on the EEG of children showing phenylketonuria.) Electroencephalography and Clinical Neurophysiology, 15(6):1036-1038, 1963.

Since there are similarities between infantile spasm and phenylketonuria, and the spasm is susceptible to ACTH treatment, four phenylketonuric children were given 40 units of ACTH per day for several weeks. Their EEG's were studied. The subjects were characterized by stereotyped motor agitation, but exhibited no epileptic convulsions. The EEG's of the subjects showed the hypsarhythmia of Gibbs. All four children had siblings with mental deficiency and phenylketonuria. One child continued to receive hydantoin and phenobarbital during the course of ACTH treatment. In two children (both 2 years old), the ACTH effect reached a maximum in approximately 2 weeks, with complete disappearance of paroxysmal activity. There was considerable improvement in the third patient's EEG, but the case was not comparable with the first two because of technical inequalities. The fourth patient showed no reaction to ACTH treatment. Following suspension of ACTH for several weeks, a new series of injections produced still greater improvement in one subject, but there was decreased effect in the other subject, together with the reappearance of paroxysmal activity during treatment. Chemical tests showed no change in the pathological quantities of metabolic products in the blood and urine after treatment with ACTH.

Governmental Hospital "Tel-Hashomer"
Haifa, Israel

1397 Tornetta, Frank J. Clinical evaluation of injectable Librium in pre-anesthetic medication. Anesthesia and Analgesia, 42(4):463-469, 1963.

This study explores further the effectiveness of chlordiazepoxide in preanesthetic medication given by the i.m. route in two situations: (1) the geriatric surgical patient, and (2) the patient undergoing dental surgery. In the first study, 190 patients over 60 years of age were divided into two groups. By random selection and double-blind design, 125 patients (87 males and 38 females) were injected i.m. with 50 to 100 mg chlordiazepoxide, together with 0.4 mg atropine sulfate, 1 hour before anesthesia. The other 65 patients (42 males and 23 females) were controls and were given atropine only. In the second study, 105 consecutive patients (49 males and 56 females, 15 to 60 years old) who were to undergo dental surgery were given 50 to 100 mg chlordiazepoxide i.m.; at the same time, 51 received atropine and 54 received 0.4 mg scopolamine. In the geriatric study, the drug decreased preoperative apprehension sevenfold as compared to controls. This was accomplished with a minimum of side effects. In the second study, a satisfactory preoperative mental state was obtained in 93.3% of the patients. When the drug was given with atropine, drowsiness occurred in 1.9% of the cases; when it was given with scopolamine, drowsiness occurred in 50%. In the total group of 230 patients, severe hypotension, respiratory depression, and vomiting were absent. The drug did not appear to augment or prolong the effects of the anesthetics. The difference in the preanesthetic mental state of the drug patients and the control group was statistically significant ($p < 0.0001$).

Montgomery Hospital
Norristown, Pennsylvania

1398 Stein, Samuel W., Lieber, Charles S., Leevy, Carroll M., Cherrick, Gilbert R., & Abelman, Walter H. The effect of ethanol upon systemic and hepatic blood flow in man. American Journal of Clinical Nutrition, 13:68-74, 1963.

An investigation was made of the effects of ethanol on the systemic and the splanchnic circulation in man. Also tested was the efficiency of a prolonged infusion of indocyanine green for the repeated determination of hepatic blood flow. The subjects

were seven male and two female patients (35 to 59 years old) who had been hospitalized with acute illness. They were all studied during convalescence. Indocyanine green in isotonic saline (stabilized in human albumin) was administered by a constant-infusion pump at a rate of from 0.4 to 0.7 mg/minute. Under control conditions, the mean hepatic blood flow was found to be 0.92 l/minute/sq m. In eight subjects in whom cardiac output was determined simultaneously, the mean hepatic flow was 0.83 l/minute/sq m and the corresponding mean cardiac output 3.38 l/minute/sq m. The mean hepatic flow fraction in these eight subjects was 0.240. During infusion of ethanol at a rate of 0.5 to 0.8 g/minute, the mean hepatic blood flow rose to 0.09 l/minute/sq m and the corresponding total cardiac output to 4.46 l/minute/sq m. The hepatic flow fraction remained essentially constant at 0.246. Ethanol had no significant effect on systemic arterial or hepatic venous pressures. Changes in calculated peripheral and splanchnic vascular resistance were inversely proportional to the effects upon flow. These results suggest that the net effect of ethanol upon the hepatic circulation is proportional to that upon the systemic circulation. Indocyanine green was quite satisfactory in the constant-infusion method of determining hepatic blood flow; it has an accuracy somewhat greater than that of sulfobromophthalein.

Harvard Medical School
Boston, Massachusetts

- 1399 Albin, Maurice S., Ordy, J. Mark, Claghorn, James L., Collins, Robert L., & Kretchmer, Henry E. **Effects of chlorpromazine on cardiovascular responses in epinephrine in surgical and psychiatric patients.** *Anesthesia and Analgesia*, 42(6): 645-651, 1963.

The effects of phenothiazine on cardiovascular responses to epinephrine were investigated in nine surgical and nine psychiatric patients. The surgical patients included three males and six females, ranging in age from 20 to 33 years. All surgical patients were free of cardiovascular or cerebral complications and had no psychiatric symptoms. The psychiatric patients included eight females and one male, ranging in age from 21 to 41 years. They were diagnosed as chronic schizophrenics and had received phenothiazines orally for a period of from 3 to 8 months, the doses ranging from 200 to 400 mg daily. Chlorpromazine was administered orally to all subjects. The surgical patients

received a single 100-mg oral dose after having received an oral placebo the previous day. The psychiatric patients had been on continuous, oral phenothiazine therapy. Ten pressure determinations at 1-minute intervals established basal cardiovascular reactivity. Ten blood-pressure determinations were made during an i.v. saline-drip infusion. A blood-pressure recording was taken 30 seconds after onset of a 1-minute epinephrine infusion at a dose level of 0.25 units per kg. A second reading was taken 30 seconds after the termination of the 1-minute epinephrine infusion. Eight additional readings were then taken during saline infusion. The mean of the basal values of the psychiatric patients did not differ significantly from the day 1 (placebo) or day 2 (chlorpromazine) values of the surgical patient. Cardiovascular differences were characterized by lower systolic pressure, higher sustained diastolic pressure, and lower pulse-rate changes to epinephrine infusion in the psychiatric patients. There are indications, however, that blood-pressure levels may be lower in some schizophrenic patients prior to medication.

Western Reserve University
Cleveland, Ohio

- 1400 Burstein, Charles L. **Respiratory effects of Benzquinamide during anesthesia.** *Anesthesia and Analgesia*, 42(4): 435-437, 1963.

Twenty orthopedic surgical patients received a dose of benzquinamide (0.25 mg per pound of body weight), which was injected into the intravenous tubing through which parenteral solution was being administered. Two minutes after the injection, an increase in the minute volume respiration was observed. This condition lasted for 20 minutes. The increase in minute volume respiration was due to both an increase in tidal volume and increased respiratory rate. A table is presented of changes in minute volume respiration in 20 cases after benzquinamide was administered. The drug also raised the arterial blood pressure. At 0.25 mg per pound, benzquinamide was found to be an effective and safe vasopressor during general anesthesia.

The New York Hospital-Cornell University
Medical College
New York, New York

1401 Lovelace, Fred R., Poe, Mary F., & Dornette, William H. L. A clinical evaluation of the antiemetic properties of thiethylperazine maleate. *Anesthesia and Analgesia*, 42(6):653-657, 1963.

Two hundred fifty-eight surgical patients received, in a double-blind study, either thiethylperazine maleate, or thiethylperazine malate, or a placebo, in order to evaluate the antiemetic qualities and any clinical differences in the two forms of the test drug. The patients ages ranges from 1 to 81 plus; 79 were males and 179 were females. The drugs were given by intramuscular injection of 2 ml, $\frac{1}{2}$ to 1 hour prior to termination of anesthesia. The effects of the drugs were evaluated during anesthesia and during the patient's stay in the recovery room. Of the 86 patients who received the placebo, 19.8% vomited and 43.0% were classified as being nauseated. With thiethylperazine maleate, 15.1% vomited (13 of 86 patients) and 25.6% complained of nausea. Seven percent (6 of 86) vomited with thiethylperazine malate and 17.4% complained of nausea. Prolonged apnea and depression were the most prominent postanesthetic complications; with the placebo and thiethylperazine maleate, there were five instances each and with thiethylperazine maleate there were six instances. In three patients, a fall in systolic blood pressure of 20 to 30 mm of mercury occurred within 10 to 20 minutes after the administration of the drug. No significant pharmacologic differences were noted between the two forms of the drug---maleate and malate.

Rutherford Hospital
Murfreesboro, Tennessee

1402 Burstein, Charles L. A cardiovascular stimulant useful during general anesthesia. *Anesthesia and Analgesia*, 42(4):429-434, 1963.

A study was made to determine the usefulness of benzquinamide in diminishing postanesthetic nausea and vomiting. In over 420 patients, 25 mg benzquinamide was injected by three routes during general anesthesia of various types (cyclopropane, barbiturate and cyclopropane, hydroxydione sodium and cyclopropane, and barbiturate and halothane). When administered parenterally, benzquinamide exerted a vasopressor effect without toxicity or an antiemetic action. When administered i.m. at the end of surgical anesthesia, postanesthetic recovery improved by diminution of the incidence of nausea, vomiting, and hypotensive episodes. When

administered i.v., it was effective in combating acute arterial hypotension due to halothane and in combating positional changes in blood pressure and certain traumatic reflex abnormalities. By this route, however, benzquinamide also caused significant cardiovascular stimulation in some patients. Three case reports are given to illustrate the vasopressor effect of i.v. benzquinamide. This effect was surprising, as the drug has been given orally in doses of from 100 to 1,000 mg/day without any adverse side effects or toxic reaction.

Cornell University Medical College
New York, New York

1403 Feldman, Robert G. & Glaser, Gilbert H. EEG study of methysergide in migraine. *Electroencephalography and Clinical Neurophysiology*, 15(4):699-702, 1963.

This communication deals with a study of the effects of acute i.v. and prolonged oral administration of methysergide on the EEG's of 11 patients (5 males and 6 females, 20 to 68 years old) with vascular headaches of the migraine type. Four patients had abnormal records. Acute i.v. administration (2, 3, or 4 mg at rates varying from 0.2 to 18.0 mg/minute) produced transitory drowsiness in 9 of the 11 patients; in the EEG's of 7, there was associated 4- to 6-cycles/second theta activity. Prolonged oral administration (4, 6, or 8 mg/day, taken for periods of up to 8 months) to four patients resulted in relief of headache in all four, but no significant change in EEG's. Previous EEG abnormalities in two of these patients remained unaltered. Of the remaining seven patients who were also on oral methysergide, four discontinued their interest in the study in the beginning, and three others dropped out after reaching high doses with occasional undesirable side effects and no clinical relief. This study, although limited in the number of observations, clearly fails to indicate any relationship among EEG abnormality, any EEG affect, and clinical response to methysergide. The drowsiness noted with the i.v. route is in contrast to the reports of jitteriness, nervousness, and insomnia made by the patients taking methysergide orally. Further work is needed to explain this opposite effect.

Yale University School of Medicine
New Haven, Connecticut

- 1404 James, I. Pierce, Derham, S. P., & Scott-Orr, D. N. **Attempted suicide—a study of 100 patients referred to a general hospital.** *Medical Journal of Australia*, 1(11):375-380, 1963.

One-hundred attempted suicides who were brought to the casualty department of Royal Perth Hospital in Australia were studied. Of these, 66 were females and 34 were males; 81% were in the 15- to 44-year-old bracket, and 19% were over 45 years old. The age and sex distribution of suicidal attempts contrasts strikingly with that of successful suicide; although attempts are over 20 times as frequent as actual suicide in women under 45 years of age, an increasingly high proportion of suicidal acts in men over 45 years of age terminate death. The diagnoses of the patients studied were psychotic mental disturbance (22%) and previous neurotic or sociopathic personality disorder (58%). Blood samples in 50 of the cases disclosed alcohol levels compatible with intoxication (over 0.15%) in 28% of the patients and levels between 0.05% and 0.15% in 34% of the patients, although many of them denied that they had been drinking. Barbiturate poisoning accounted for 55% of the cases of those who attempted suicide by an overdosage of drugs. There were 85 cases of drug overdosage. The acts were impulsive in 66%, 15% had been planned, 11 of the patients claimed to have no recollection of the incident, and 8 denied any suicidal intent (although circumstances usually suggested otherwise). About 30% had attempted suicide previously, and three patients subsequently committed suicide within 6 months of inclusion in the study. One-third of the patients had previously been under psychiatric care, and 20% had been seen by a psychiatrist less than a month before the attempt. The number of patients subsequently hospitalized was 12%; 36% were referred to inpatient psychiatric care, 19% to the psychiatric outpatient clinic, and 32% discharged themselves from the hospital or were discharged. It is recommended that all patients who come into medical care because of a suicidal attempt should be given a full psychiatric examination and assessment, and if necessary, admitted to hospital until this is done.

Royal Perth Hospital
Sydney, Australia

- 1405 Hartigan, G. P. **The use of lithium salts in affective disorders.** *British Journal of Psychiatry*, 109(463):810-814, 1963.

Over the period 1957 to 1963, 45 patients suffering from affective disorders and being treated with lithium salts were assembled. The diagnostic categories were as follows: manic-depressive patients (12); manic patients (20); depressive patients (8); and manic-depressive personality (5). Lithium was given orally as the carbonate, in initial dosages of from 300 to 1,800 mg daily. Ten brief case reports from the various diagnostic categories are presented. Encouraging clinical results have been obtained in cases of recurrent depression as well as in manic-depressive and manic cases.

St. Augustine's Hospital
Canterbury, England

- 1406 Marcus, Phillip S. & Pelaez, Francisco A. Gutierrez. **Evaluation of a premedicant.** *Anesthesia and Analgesia*, 42(5):542-546, 1963.

A technique for the evaluation of a premedicant in facilitating and decreasing the time necessary for anesthetic induction is described. It is simple, practical, and reproducible. Significant differences can be demonstrated in the speed of induction by varying the premedicant used. Three groups of 25 patients each, all being readied for multiple dental extractions with alveolectomy, were used. Their average ages were 29.9, 31.6, and 29.8 years, respectively; 33 were males and 42 were females. Group A received 25 mg meperidine and 100 mg hydroxyzine HCl; group B received 50 mg meperidine; and group C received 25 mg meperidine. All patients received 0.6 mg atropine with one of the premedicants about 1 hour before surgery. The patients then were anesthetized with oxygen, nitrous oxide, and halothane. Induction was accomplished using the semiclosed technique. The end point was taken at the time of disappearance of the eyelid reflex; the appearance of a fixed, central, small pupil; and the resumption of regular and rhythmical breathing. The time was recorded from the time the mask was put on until the anesthesiologist stated that his end point was reached. He was unaware of the premedication; thus, the study was blind. The most rapid induction was obtained in group A (4.46 minutes average).

time); group B was next (average time 5.19 minutes), and then group C (average time 6.21 minutes).

Boston City Hospital
Boston, Massachusetts

- 1407 Hordern, Anthony, Holt, N. F., Burt, C. G., & Gordon, W. F. **Amitriptyline in depressive states. Phenomenology and prognostic considerations.** *British Journal of Psychiatry*, 109(463):815-825, 1963.

An inpatient investigation using blind techniques of the phenomenology and treatment of 137 hospitalized female depressives is described, in which amitriptyline was compared with imipramine. The dosage for both drugs was 150 mg/day for 1 week, then 200 mg/day for 3 to 5 weeks. Using hospital discharge without EST as the criterion of success, amitriptyline, which relieved 81% of the patients, was superior to imipramine, which relieved 54%. Four symptoms increased significantly with age and five increased disproportionately with increasing overall severity. Five sets of prognostic variables were studied for the 2 drug groups and for 12 comparable subgroups delineated by age and severity of illness. These variables were: (1) the Hobson scale score; (2) the initial severity of the depressive symptoms; (3) the presence of delusions; (4) the effects of age, menopausal state, and type and severity of depression; and (5) the response to 1 week of treatment. Patients successfully treated with amitriptyline spent no more time in the hospital than did a matched retrospective control group treated with EST. The practical implications from this study would seem to be: (1) depressed patients with unequivocal depressive delusions should be given EST; and (2) other depressives should be given amitriptyline. Of an 10 patients, 8 or 9 can be expected to recover in 4 to 6 weeks, and 6 or 7 will improve significantly within the first week of treatment. At this time, failure to improve in anorexia, middle insomnia, and reduced work and interests should be taken as an indication for alternative treatment.

Mental Health Research Institute
Victoria, Australia

- 1408 Greene, Nicholas M. **Preanesthetic blood pressure determinations: An analysis of 2189 cases under clinical conditions.** *Anesthesia and Analgesia*, 42(4):454-462, 1963.

This study was instituted to obtain information on preanesthetic changes in blood pressure that may be expected to occur normally under clinical conditions and to determine whether, under clinical conditions, the type of preanesthetic medication significantly influences blood pressure. Arterial blood pressures were determined in 2,139 elective surgical patients (aged 14 to over 70 years) at the time of admission to the hospital, early in the morning prior to surgery and premedication, and, in 1,934 cases, following preanesthetic medication. The premedicants and their dosages (per 70 kg body weight) were: barbiturates alone, 75 to 125 mg; barbiturates when given with a narcotic, 50 to 100 mg; meperidine alone, 75 to 100 mg; meperidine when used with a barbiturate, 50 to 100 mg; morphine alone, 8 to 10 mg; morphine when used with a barbiturate, 6 to 10 mg; scopolamine, 0.3 to 0.5 mg; and atropine, 0.4 to 0.6 mg. Comparison of admission blood pressure and resting blood pressure showed a significant decrease in blood pressure in all age groups associated with the resting state. Comparison of resting blood pressure and post-premedication blood pressure showed a tendency for the blood pressure to rise after premedication in normotensive patients and a tendency for the blood pressure to decrease in hypertensive patients, the statistical significance of the changes being related to age. There was no difference in blood-pressure response whether premedication consisted of a barbiturate, a narcotic drug, or a barbiturate plus a narcotic drug.

Yale University School of Medicine
New Haven, Connecticut

- 1409 Roos, Björn-Erik. **The effect of monoamine oxidase inhibitors on the level of 5-hydroxyindoleacetic acid in human cerebrospinal fluid.** *Life Sciences*, 2(1):1-4, 1963.

To test the hypothesis that an increase in the concentration of 5HT, noradrenaline, and dopamine and a decrease of MAO activity in the cerebrospinal fluid after administration of an MAO inhibitor may be reflected as a decrease in the level of 5HIAA was tested. Two female patients (A and B), 52 and 47 years old, respectively, who were suffering

from chronic schizophrenic-like psychoses were studied. They were prescribed MAO therapy in order to activate them. Before treatment, control samples of cerebrospinal fluid were taken. Then a dose of 200 mg/day nialamide was given for 10 days (patient A) and 6 days (patient B), and cerebrospinal-fluid samples were again taken. Two months later, the patients were given 100 mg/day iproniazid for 12 days and, samples were taken as before. All the cerebrospinal-fluid samples were analyzed for 5HIAA. There was no change in the values of 5HIAA from the control to the treatment samples. Under treatment, the patients were restless and more active, but they were not less autistic and their inability to contact was unchanged.

University of Göteborg
Göteborg, Sweden

- 1410 Marx, Gertie F., Saifer, Abraham, & Orkin, Louis R. **Cerebrospinal fluid cells and proteins following spinal anesthesia.** *Journal of Anesthesiology*, 24(3): 305-312, 1963.

This study was designed to determine the changes in cerebrospinal-fluid proteins or cell content following specific local anesthesia and to evaluate a possible relationship between blood and cerebrospinal-fluid proteins. A total of 58 patients (15 to 84 years old) who were receiving spinal anesthesia for relatively minor operations were studied. Samples of blood and cerebrospinal fluid were taken before and after lumbar puncture or local anesthesia. The anesthetics used were tetracaine-dextrose, tetracaine-dextrose-epinephrine, procaine, dibucaine-dextrose, and lidocaine-dextrose. Total protein, albumin, and globulin determinations in 45 cerebrospinal-fluid samples taken 1 to 18 days after spinal anesthesia showed mild to moderate fluctuations that were similar to fluctuations in the blood samples collected simultaneously. Cerebrospinal fluid obtained 1 and 4 days, respectively, after a complaint by two patients of leg pain during lumbar puncture showed marked increases in protein, but blood-protein values declined. Protein analysis by electrophoresis on cerebrospinal fluid prior to and 3 or 6 days after spinal anesthesia revealed normal patterns without changes when four different anesthetics were used. Cerebrospinal-fluid cell counts in samples taken prior to and 12 and 24 hours after spinal anesthetics showed an increase in red blood cells in both preanesthetic and post-

anesthetic specimens, but no change in white cells. No cerebrospinal-fluid protein or cell changes developed that were due specifically to uneventful lumbar puncture or to injection of the anesthetic.

Yeshiva University
New York, New York

- 1411 Hocking, Frederick. **Methohexital sodium: a new ultra-short-acting intravenous anaesthetic agent for use in electroconvulsive therapy.** *Medical Journal of Australia*, 1(2):37-40, 1963.

This report begins with a discussion of the methods of producing transient anesthesia before EST. Two drugs, thiopentone sodium and methohexital sodium, that have been used as anesthetics are compared, and their chemistry and pharmacology are described. (A figure is given of the structure of methohexital.) The action of methohexital on extravascular tissue is discussed from the literature, and a synopsis of published clinical surveys of methohexital in EST is presented. The results of a survey by the author of the use of methohexital in 72 patients (20 to 72 years old) who received 623 EST treatments (1 to 26 treatments per patient) are also presented. The initial dosage of methohexital used was 100 mg (10 ml), but it was found that transient anesthesia of satisfactory depth and duration could be obtained with 45 mg (4.5 ml). The procedure was to inject 4.5 ml of the drug; then, provided that the patient was asleep, 1 ml (75 mg) of suxethonium bromide (a muscle relaxant) was given, followed immediately by EST. In only two cases was it necessary to inject more than 4.5 ml to produce sleep. Despite the small dosage, no complaints were made after treatment of the awareness of paralysis or inability to breathe. The induction of sleep was smooth, and there were no complaints of unusual odor or taste. The most outstanding feature of the drug is the rapidity with which its anesthetic effect was dissipated. Every patient could be roused within 5 minutes of completion of treatment, with no evidence of confusion after a further 5 minutes. Methohexital may be the most satisfactory drug yet for the production of anesthesia in EST.

Melbourne, Australia

- 1412 Holderness, Margaret C., Chase, Patricia E., & Dripps, Robert D. **A narcotic analgesic and a butyrophenone with nitrous oxide for general anesthesia.** *Journal of Anesthesiology*, 24(3):336-340, 1963.

A technique of general anesthesia using phentanyll, a potent analgesic, and dehydrobenzperidol, a butyrophenone derivative, i.v., together with the inhalation of nitrous oxide, has been used to anesthetize 400 patients, 15 to 92 years of age, for general surgical procedures. The optimal mixture contained 1 mg/ml dehydrobenzperidol and 0.02 mg/ml phentanyll (50:1). Preanesthetic medication was widely varied, but no narcotics were used. The method afforded excellent analgesia and hypnosis for operations not requiring muscle relaxation. When muscle relaxation was needed, d-tubocurarine was given in doses similar to those used in thiopental-N₂O-curare techniques. Circulatory stability was impressive both during and after surgery. Respiratory depression resembled that seen when other narcotic analgesics are used as adjuvants to anesthesia, but it was of lesser duration than with most of the others. Rigidity of skeletal muscles, occasionally making pulmonary ventilation difficult, but responding promptly to small doses of relaxants, was seen primarily when excessive amounts of the mixture had been given by vein. Postoperative nausea occurred in 23 patients, but lasted no longer than 12 hours in any case. The anesthetic technique provides profound analgesia, minimal hypotension, protection against epinephrine-induced ventricular rhythms, and an apparently lessened incidence of postoperative nausea and vomiting.

University of Pennsylvania Schools of Medicine
Philadelphia, Pennsylvania

- 1413 Dwyer, Brian & Gunner, B. W. **Phenacetin cyanosis, barbiturate habituation and cardiac arrest.** *Medical Journal of Australia*, 1(1):13-14, 1963.

The case history is presented of complications following anesthesia in a 28-year-old woman who was taking large quantities of salicylates, codeine, phenacetin, caffeine, barbiturates, and alcohol prior to admission for surgery. The patient received 100 mg pethidine and 0.4 mg scopolamine as premedication. Anesthesia was induced with 200 mg thiopentone and 40 mg d-tubocurarine chloride. The patient was unexpectedly tolerant

to nondepolarizing muscle relaxants, which caused obstruction to lung inflation, extreme difficulty in intubation, anoxia, and cardiovascular depression. The difficulties arising from the patient having cyanosis due to sulfhemoglobinemia and methemoglobinemia, which resulted from excessive use of drugs, are discussed. The advantages of external cardiac massage for treatment of clinical cardiac arrest are described.

St. Vincent's Hospital
Sydney, Australia

- 1414 Aston, Roy, Dan, Kenjiro, & Greifenstein, F. E. **Effect of anesthesia upon venous 5-hydroxytryptamine levels.** *Anesthesia and Analgesia*, 42(6):624-631, 1963.

Forty patients of both sexes (16 to 82 years of age) were studied to determine whether venous whole-blood levels of 5HT are influenced by various anesthetic procedures. Anesthesia was induced by thiamyl sodium i.v., cyclopropane, halothane, and intrathecal tetracaine. No significant changes in 5HT were observed except in those cases of spinal analgesia higher than the seventh thoracic segment. In this group of eight patients, there was a consistent and significant decrease in 5HT values. It is suggested that these results are due to splanchnic pooling secondary to sympathetic blockade. Levels of 5HT found in halothane anesthesia showed a range, both above and below control values, about twice that seen with the other general anesthetic agents employed in this study. The suggestion is made that, since many of these patients were allowed to ventilate spontaneously, an increase in venous 5HT may have been due to respiratory acidosis. Transient, but severe, depression of hepatic function may also have contributed to such a finding. Decrease in 5HT blood levels may have been the result of halothane-induced sympathetic blockade with splanchnic pooling.

Wayne State University College of Medicine
Detroit, Michigan

- 1415 Frame, M. C. **The use of "Pertofran" in depression: A short communication.** *Medical Journal of Australia*, 2(9):356-357, 1963.

The effects of desmethyylimipramine, a metabolite of imipramine, were tested in 39 female and 12 male patients (25 to 69 years of age), who were suffering from a variety of

illnesses, with depression being the major symptom. The target symptoms chosen to determine drug effect were inhibition, agitation, dysphoria, anxiety, somatic complaints, and insomnia. The patients received 25 mg of the drug p.o., t.i.d. initially, with increases of 25 mg on successive days if there was no response by the third day of treatment. A good response was achieved in 38 of the 51 patients, with manic depressive and involutional melancholic categories responding most favorably. Onset of improvement was more rapid than with imipramine. Side effects were fewer and less severe than those of imipramine. Exacerbation of symptoms was seen in five patients 14 days after initial improvement; all five cases responded to imipramine. Desmethylinipramine was judged to be as potent as imipramine, and it has the advantage of producing less severe side effects.

Mental Hospital, Parramatta
New South Wales, Australia

- 1416 Matteo, Richard S., Katz, Ronald L., & Papper, E. M. **The injection of epinephrine during general anesthesia with halogenated hydrocarbons and cyclopropane in man.** *Journal of Anesthesiology*, 24(3):327-330, 1963.

The effects of subcutaneous injection of epinephrine in precipitating cardiac arrhythmias during cyclopropane-oxygen anesthesia were studied. One-hundred control patients and 70 test patients were selected. Premedication consisted of a barbiturate and a belladonna drug; in 25% of the patients, meperidine (25 to 75 mg) was added to this combination. Anesthesia was induced with 125 to 375 mg of 2.5% thiopental; d-tubocurarine was the sole supplemental drug used after induction. Following thiopental, cyclopropane (500 ml/minute) and oxygen (500 ml/minute) were given; the flow was then maintained at 50 to 200 ml/minute cyclopropane and 250 to 500 ml/minute oxygen. In the 70 test patients, epinephrine was injected at 5-minute intervals to a total dose of 30 ml (0.5 mg). Ventricular arrhythmias appeared in 11% of control patients. The subcutaneous injection of epinephrine during cyclopropane-oxygen anesthesia caused ventricular arrhythmias in 30% of the test patients studied, despite careful attention to adequate ventilation and depth of anesthesia. This finding is contrasted with the low incidence of arrhythmias in similar studies

with nitrous oxide--trichlorethylene or halothane anesthesia. Possible explanations for these differences are discussed.

Presbyterian Hospital
New York, New York

- 1417 Irvine, R. O. H., Montgomerie, J. Z., & Spence, M. **Assisted respiration, noradrenaline infusion and the artificial kidney for glutethimide ("Doriden") poisoning.** *Medical Journal of Australia*, 2(7):277-279, 1963.

A case of glutethimide poisoning following injection of 60 (15 g) tablets of the drug is reported in a 33-year-old man. Treatment consisted of assisted respiration, noradrenaline infusion, and use of the artificial kidney. Glutethimide poisoning is difficult to treat because the drug induces sudden episodes of apnea, frequent severe hypotension, and cyclical variation of CNS depression. The artificial kidney is helpful in removing the drug from the circulatory system.

Auckland Hospital
Auckland, New Zealand

- 1418 North, William C., Collawn, Thomas H., Hudnell, A. B., Jr., & Stephen, C. R. **Postoperative vomiting: Influence of thiethylperazine.** *Anesthesia and Analgesia*, 42(5):559-565, 1963.

The antiemetic action of thiethylperazine was evaluated using a double-blind method in three groups of postoperative patients. Groups 1 and 2 were comprised of 1,390 and 1,336 unselected surgical patients, respectively, and Group 3 had 200 ophthalmologic-surgery patients. The drug, administered by i.m. injections, reduced the incidence of postoperative vomiting significantly. Its therapeutic action was most apparent in patients who, by virtue of age, sex, race, type of operation, or anesthetic agent employed, were more prone to vomit; its action was seen with greatest clarity in the group of ophthalmologic patients. The optimal intramuscular dosage of thiethylperazine is 10 mg. The duration of action of a single dose is not longer than 4 hours; repeated administration at intervals of 4 hours is safe. In the dosages administered, the antiemetic is free of deleterious side effects.

Duke University Medical Center
Durham, North Carolina

1419 Reid, A. Arnaud. The effect of phenmetrazine upon the body weight of unselected mental hospital patients. *Medical Journal of Australia*, 2(7):274-276, 1963.

A double-blind study was done in randomly selected, chronic mental-hospital patients, who were not on any dietetic regimen, to test the weight-reducing properties of phenmetrazine. Sixteen patients received phenmetrazine (25 mg b.i.d.) and 19 received placebo for 7 weeks. No significant difference was found in weight loss between the two groups. When patients receiving chlorpromazine were excluded from the analysis, however, phenmetrazine-treated patients showed a significant weight loss, but the size of the sample was too small to make any valid conclusions on the effectiveness of phenmetrazine as a weight-reducing agent. The possibility that chlorpromazine antagonizes the action of phenmetrazine is discussed. The literature on the weight-reducing properties of phenmetrazine is briefly reviewed.

Plenty Mental Hospital
Victoria, Australia

1420 Perez-Borja, Carlos & Rivers, Morris H. Some scalp and depth electrographic observations on the action of intracarotid sodium amytal injection on epileptic discharges in man. *Electroencephalography and Clinical Neurophysiology*, 15(4):588-598, 1963.

Five epileptic patients were studied with 10 intracarotid injections of sodium amytal during scalp and/or depth electrographic recordings. In 8 of the 10 injections, the dose of amytal was 100 mg; in one case 50 mg was used, and in the other, 150 mg. Observations on secondary bilateral synchrony were in accord with previous studies, indicating that an injection in the carotid homolateral to the triggering focus suppresses or depresses discharges on both sides, whereas injection on the contralateral carotid does not modify them or slightly reduces the amplitude only on the hemisphere ipsilateral to the injection. Observations on temporal lobe epilepsy indicated that the results are very complex. Injection of amytal into the carotid of one side could produce either suppression of an ipsilateral focus or activation of the ipsilateral or the contralateral focus. These effects appear, however, to be due to the action of the drug itself rather than to sleep or drowsiness.

Rochester State Hospital
Rochester, Minnesota

1421 Markham, Charles H., Clark, William G., & Winters, Wallace D. Effect of alpha-methyl dopa and reserpine in Huntington's chorea, Parkinson's disease and other movement disorders. *Life Sciences*, 2(9):697-705, 1963.

Observations were made on the effects of α -methyldopa and reserpine in the treatment of Huntington's chorea, Parkinson's disease, and other dyskinesias to help elucidate the role of the biogenic amines in the chorea syndrome. Reserpine, which depletes serotonin, dopamine, and norepinephrine, is known to be effective in treating chorea patients. Alpha-methyldopa produces only a transient depletion of serotonin and dopamine, but markedly depletes norepinephrine. Ten patients with Huntington's chorea (aged 22 to 57 years), six patients with Parkinson's disease (aged 42 to 68 years), and eight patients with various dyskinesias (aged 19 to 65 years) were observed on an outpatient basis for 1 to 3 years. Reserpine (1 mg/day p.o.) was given to all 24 patients. No change was noted in the parkinsonian or dyskinetic patients, but 7 of the 10 chorea patients showed improvement in abnormal movements. Alpha-methyldopa (1,050 to 3,250 mg/day) was given to all 24 patients. No response was observed. From these data, norepinephrine is not a significant factor in Huntington's chorea.

UCLA Center for Health Sciences
Los Angeles, California

1422 Sutherland, John M. & Bowman, Dorothy A. Sulthiame ("Ospolot") in the treatment of temporal lobe epilepsy. *Medical Journal of Australia*, 2(13):532-534, 1963.

Twenty-nine patients suffering from temporal lobe epilepsy, who previously had been inadequately controlled by other drugs or combinations of drugs, were given sulthiame in addition to the existing drug therapy. There were 19 male and 10 female patients, with ages ranging from 4- $\frac{1}{2}$ to 50 years. The initial dose was 0.2 g, b.i.d., the dose being then increased by gradual increments until adequate control was achieved or until a maximum dose of 1.2 g, t.i.d., was being given. At 0.2 g, b.i.d., one patient was found to be significantly improved, and in one case the drug was withdrawn because of side effects. At 0.3 g, t.i.d., one patient was controlled, one was significantly improved, and one showed no improvement. At 0.4 g, b.i.d., one patient showed improvement. At 0.6 g, t.i.d., 3 patients

were controlled, 10 showed improvement, 1 showed no improvement, and 3 showed unfavorable side effects; the drug was withdrawn. At 0.8 g, q.i.d., two patients were controlled, and two patients were significantly improved. At 1.2 g, t.i.d., one patient was improved, and one patient showed no improvement. The side effects included paraesthesia in the extremities, headaches, giddiness, and unsteadiness. Hematological studies, urine analysis, and liver-function tests showed no abnormal features. Sulthiame was found, in some instances, to have a tranquilizing effect.

Brisbane Hospital
Brisbane, Australia

- 1423 Vencouský, E., Petrová, E., Šedivec, VI., Janovský, Fr., & Dvořáková, M. *Předběžné klinické zkušenosti s léčbou Sordinolem. (Preliminary clinical experience with sordinol.)* *Activitas Nervosa Superior*, 5:198-199, 1963.

The reportedly good therapeutic effect of the piperazine derivative of chlorprothixene, chlorpenthixol (Sordinol), especially in paranoic-hallucinatory and manic syndromes, was evaluated in 14 patients, including 9 females and 5 males, 20 to 58 years old, with average age 36.7. Their diagnoses were paranoic hallucinations in 9 patients, productive catatonia in 2, amentia in 2, and depression in 1. Daily dosage for most patients was 150 to 300 mg, attaining 450 mg in 3 patients. The duration of therapy ranged from 15 to 38 days, with average duration 28 days. Clinical evaluations were made by rating scale. The psychopathological symptomatology improved in 9 patients; total remission occurred in one patient with amentia, and the remaining eight patients showed general clinical improvement. Hallucinations were corrected in all but one patient. Of the side effects, extrapyramidal symptomatology was most frequent, occurring in 9 patients. Hypotension was observed in 6 patients. In therapeutic doses, chlorpenthixol produced a synchronizing effect in the EEG, as well as inhibition of modification of afferent sensory signals.

K. University
Plzen, Czechoslovakia

- 1424 Bizzarri, Dante, Giuffrida, Joseph, Fierro, Frank E., & Latteri, Francis S. *Preanesthetic medication with intramuscular administration of hydroxyzine hydrochloride: A parallel, double-blind study of hydroxyzine hydrochloride, meperidine hydrochloride, hydroxyzine hydrochloride and meperidine hydrochloride, secobarbital sodium, and a placebo.* *Anesthesia and Analgesia*, 42(3):316-324, 1963.

Preanesthetic medication was given i.m. to 462 patients admitted for surgical treatment in a period of 10 months. Seventy-eight patients were between 10 and 30 years of age, 177 were between 30 and 50 years, 117 were between 50 and 70, and 58 were 70 or more years of age. Five ml of a solution of one of the following trial substances was administered i.m. as a premedicant: (1) hydroxyzine, 150 mg; (2) hydroxyzine, 150 mg and meperidine, 50 mg; (3) meperidine, 50 mg; and (4) secobarbital, 100 mg and a placebo (physiologic saline). The double-blind method of control was used throughout the study. There was no significant difference in the pulse rate in cases in which a drug or a placebo was administered but when meperidine was administered alone, there was a significant difference. Upon questioning regarding their feelings, the proportion of unfavorable responses was lower when meperidine had been administered. Administration of a drug as a premedicant brought fewer unfavorable responses than did a placebo. Unquestionably, hydroxyzine is of use in the practice of anesthesiology. It has most of the advantages of other premedicants without some of their disadvantages.

New York Medical College
Metropolitan Medical Center
New York, New York

- 1425 Ríkovský, Š., Náglová, R., & Zapletálek, M. *Naše zkušenosti s použitím Theralenu v psychiatrii. (Our experience with the use of Theralene in psychiatry.)* *Activitas Nervosa Superior*, 5:199-200, 1963.

Theralene, or alimenazine, in liquid form was given to six adult patients, 20 to 40 years old, average age 31, with diagnoses of paraphrenic (1) and paranoic (5) schizophrenia. The patients were given 300 to 500 mg/day alimenazine for 5 days, followed by placebo for 5 days, over a period of 20 days. Clinical rating showed improvement mainly in unrest, feelings of inadequacy, and social adaptation. All patients showed side effects, mainly tachycardia, dry mouth,

weakness, and hypersalivation. Laboratory findings were unchanged. Alimenazine in syrup form was given to 18 children, 6 to 13 years old, including 7 with neurasthenia, 5 with neurotic tic, 3 with hysteria, 1 with anxiety neurosis, and 2 with dysharmonic character development. The patients were given 5 to 10 ml (2.5 to 5 mg) alimenazine syrup t.i.d. for 5 days, followed by placebo for 5 days, in two successive series. No change in the psychopathological picture was observed with either drug or placebo. Seven children of this group were then given 10 mg five times daily for seven days, but no noticeable therapeutic effect was produced. No hypnotic effect was observed during the day. The laboratory data showed no change. Alimenazine is slightly less active than chlorpromazine in regard to controlling hallucinations, and it has greater hypnotic effect than the latter.

Psychiatric Hospital
Sternberk, Czechoslovakia

- 1426 Zapletálek, M., Říkovský, Š., Rychlá, D., Strnad, M., Horák, L., Hříbal, R., & Stepanova, M. **Klinické a ambulantní zkušenosti s terapií Majepilem. (Clinical and ambulatory experience with Majepil therapy.)** *Activitas Nervosa Superior*, 5:200-201, 1963.

A group of 23 chronic schizophrenic inpatients were treated with thioproperazine for 7 weeks, partly by the usual method, but mainly by the discontinual method. The average age of the patients was 31, their average duration of illness 8 years (2 to 15 years), and their dosage was 7.0 mg/day. As a result of this course of treatment, nine patients were discharged, six showed great improvement, and no substantial change was noted in eight patients. Laboratory tests, including tests of liver function, were not significantly influenced by the treatment. Side effects included akathisia, automatic gait, and pronounced hypertonic-hypokinetic reaction. Marked psychomotor disturbance in three cases was not influenced by injections of 90 to 150 mg thioproperazine per day, and other ataractics had to be used. A word test of six patients showed improvement in latent period. The potassium-calcium quotient showed pronounced vagotonia in five patients. In one chronic schizophrenic, neither the above quotient nor the clinical picture showed any change. Seven ambulatory patients also were tested. Four of these patients were given 2 to 10 mg/day of thioproperazine, and three received 2 to 5 mg/day, plus 100 mg chlorpromazine or 1 mg re-

serpine. At a dosage of 10 mg, the subjective complaints of this group were general weakness and depressed motor activity. Objectively, they showed increased interest in their jobs and improved sociability.

Psychiatric Hospital
Sternberk, Czechoslovakia

- 1427 Cooper, T. B. & Cranswick, E. H. **Iodoamino acid distribution in the serum of schizophrenic patients receiving perphenazine.** *Life Sciences*, 2(7):527-531, 1963.

Seven male patients, diagnosed as chronic schizophrenics, were selected for this study. These patients were undergoing continuous perphenazine therapy for periods of 10 months to 4 years, and the PBI₁₂₇ was elevated above 9 mcg/100 ml. Five males within the same age group, who were not receiving any form of medication, were used as normal controls. Patient controls were two male chronic schizophrenics (of the same age group) on the same ward, who had never received perphenazine and had not received any medications for the previous 8 years. Large amounts of noniodothyronine iodine was found in the patients receiving perphenazine, whereas none was found in the patients not receiving the drug. The absence of thyrotoxicosis is confirmed by a nonelevated neck uptake of iodine¹³¹ and conversion ratios, and by erythrocyte uptakes of T₃ iodine¹³¹ within the normal range.

Rockland State Hospital
Orangeburg, New York

- 1428 Puflett, R. D. **Epilepsy.** *Medical Journal of Australia*, 1(20):731-733, 1965.

Major and minor epilepsy are discussed, with rehabilitation as the main concern. A survey of 100 epileptic patients in the Commonwealth Rehabilitation Service found that the patients fell into 3 groups: those with major epilepsy, 82 persons; those with minor epilepsy, 9 persons; those with psychomotor epilepsy and other types, 9 persons. The average age of onset of major epilepsy is about 10- $\frac{1}{2}$ years. The treatment of major epilepsy has been with (1) phenobarbital; (2) diphenylhydantoin sodium; (3) either or both of these drugs combined with primidone; (4) one or combinations or all of the previously

mentioned drugs with methoin. The absence of an aura produces a medical complex which makes employment impossible. Unless control can reduce the frequency of fits to one in 6 months, employment is not likely to be found. The age of onset of minor epilepsy is about 12 years. Troxidone is generally the drug of choice for the treatment of minor epilepsy. Minor epilepsy can be a major cause of hysterical reactions, but with careful diagnosis and appropriate treatment, the patient may be able to hold a job.

Commonwealth Rehabilitation Service
Australia

1429 Guile, Leslie A. Rapid habituation to chlordiazepoxide ("Librium").

Medical Journal of Australia, 2(2):56-57, 1963.

A case report is given of a rapid habituation to chlordiazepoxide in a 44-year-old woman outpatient who was first prescribed the drug (10 mg q.i.d.) because of irritability, depression, and manifest anxiety. After 3 days, she was much calmer, and the prescription was repeated. Two weeks later, she had an exacerbation of her condition and the dosage was increased to 20 mg t.i.d. Ten days later she asked for more capsules, stating that she had taken up to 80 mg/day on some days but felt well, calm, socially active, and tension-free. The medication was continued, with a warning against a further increase in dosage. Twenty-five days later, the patient returned to the clinic with her husband and confessed she was taking as many as 12, 14, and 16 capsules daily. She said she never had so much confidence; she was poised, mildly euphoric, and showed no manifest anxiety. Her only complaint was a loss of weight—she had no appetite at all. There were no complaints of drowsiness or ataxia, and no somatic symptoms. There was a fine tremor of her outstretched hands and her pupils were slightly dilated but reacted normally. With difficulty she was persuaded to return her supply of chlordiazepoxide, and trifluoperazine (5 mg b.i.d.) was substituted. There was a dramatic change in the patient—she was depressed, agitated, and lost all her confidence. Her appetite resumed, however, and her anxiety seemed to be under control. A count of the returned chlordiazepoxide capsules revealed that she had been taking an average of 14 daily. The patient had no history of drug-dependence or overconsumption of alcohol, and she did not fit the description of the "drug-dependent personality." It appears

that chlordiazepoxide is not without toxic manifestations, both acute and chronic, and continued clinical vigilance is necessary.

Alexandra Clinic
Victoria, Australia

1430 Lance, J. W., Fine, R. D., & Curran, D. A. An evaluation of methysergide in the prevention of migraine and other vascular headaches. Medical Journal of Australia, 1(22):814-818, 1963.

A lysergic acid derivative, methysergide, was subjected to clinical trial in a series of 200 patients (9 to 75 years old) suffering from severe and frequent vascular headaches. The treatment was double-blind; two tablets of either methysergide (1 mg/tablet) or placebo were prescribed t.i.d. for 1 month. The improvement with methysergide was statistically highly significant in patients with migraine, but was not significant in patients whose vascular headaches were associated with tension headache. Of the 150 patients with migraine treated with methysergide, 24% became free of headache and a further 40% were "substantially improved." Fifty-three patients have now taken methysergide continuously for periods of 3 to 9 months, and all except five have maintained their initial improvement. (Maintenance dose was one tablet t.i.d.) There was no feature of the history that could predict which patients would respond to methysergide and which would not, but it was noted that diarrhea was more commonly associated with the migraine attack in the latter group. Five out of seven patients with Horton's syndrome ("cluster headaches") showed considerable improvement with methysergide. Side effects were experienced by 36% of patients on starting treatment, but these were mostly transient. The drug had to be discontinued, however, in 9% of cases in which side effects were severe. It is recommended that methysergide should be reserved for those patients who continue to have frequent attacks of migraine in spite of other forms of treatment, and that dosage should be started cautiously with 1 mg t.i.d. after meals to minimize the incidence of side effects. The possible mechanism of action of the drug is discussed in relation to its known effect as a serotonin antagonist.

Prince Henry Hospital
Sydney, Australia

- 1431 Bartholomew, Allen A. **Perphenazine ("Trilafon") in the immediate management of acutely disturbed chronic alcoholics.** Medical Journal of Australia, 1(22):812-814, 1963.

The assessment of perphenazine in the management of the alcoholic who is difficult, aggressive, and suffering from retching, nausea, and vomiting is described. Over a 15-month period, 100 patients were given 2 ml (10 mg) i.m. and, as soon as possible after that, 4 mg every 4 hours orally for 24 hours, followed by 4 mg t.i.d. This technique allowed a quick response from the i.m. injection and a prolonged effect from taking the drug orally. (Previous treatments with lower dosages and with i.m. injections only were not adequate.) All patients received additional general treatment (bed rest, vitamin B complex, fluids, sugar, etc.). Fourteen patients left the clinic before it was possible to assess the drug. Of the 86 patients who remained, all were clearly helped by the drug and the total regimen. Sleep or marked drowsiness was apparent after about 15 to 30 minutes, and, when the patient was asleep, he was easily roused. This aids in the application of the additive care. After being roused, the patient would rapidly fall asleep again. An impressive aspect of perphenazine was its antiemetic properties. The patients themselves were impressed by the rapidity of its action. In addition, the drug was safer and freer of serious side effects than all others tested previously. In two cases, there were convulsions of moderate severity.

Alexandra Clinic
Victoria, Australia

- 1432 Mackay, Ian R. & Langford, Ida. **Blood alcohol estimations in patients attending an out-patient clinic.** Medical Journal of Australia, 1(21):778-779, 1963.

This paper describes the results of 127 blood-alcohol-level estimations in 75 adult patients (57 males and 18 females, 33 to 77 years old) from an outpatient clinic who were selected on the basis that an excessive alcohol intake was possibly playing some part in their illness. A level above 0.010 g of alcohol per 100 ml of blood was regarded as a positive unit. Alcohol was detected on at least one occasion in the blood of 31 (41%) patients. Concentrations ranged from 0.010 to 0.325 g/100 ml blood. Twenty-seven patients were tested more than once;

of these, 18 had negative results at first but, upon further testing, 8 had a subsequent positive result. The incidence of positive results according to the degree of alcoholism, the presence of diseases associated with alcoholism, and the sex of the patient are tabulated. The patients were divided into three groups: chronic alcoholics, heavy drinkers, and those in whom alcohol intake was uncertain. The incidence in males was greater than in females, but there were more males than females to begin with. This study illustrates the application of blood-alcohol testing to a selected population in which information regarding drinking behavior is desired. The data presented also emphasize the intractable nature of the alcohol habit and the relative ineffectiveness of medical counseling in its control. Patients who arrived at the clinic drunk or with high blood-alcohol levels had a poor prognosis with regard to cure, domestic harmony, future employability, and maintenance of health.

Royal Melbourne Hospital
Melbourne, Victoria, Australia

- 1433 Howe, G. D. **A new non-irritant analgesic.** (Letter) Medical Journal of Australia, 2(5):210, 1963.

A double-blind trial of an analgesic, alloxiprin, and a placebo was made in 18 patients suffering mainly from arthritis and its allied conditions (16 patients) and migraine (2 patients). Nine patients (five females and four males, 45 to 79 years old) were given the active drug and nine patients (six females and three males, 45 to 73 years old) were given placebo. (Dosage is not given.) The patients were asked to report at a later date on the effectiveness of the medication. A brief summary of each patients' response is given. The impressions and notes were made before the code was released to the examiner. Both preparations were remarkably free of gastric irritation. Alloxiprin gave effective analgesia in eight out of the nine cases. The placebo was ineffective in six cases, slightly analgesic in one case, and effective in two cases. In one case, it caused some gastric irritation. Alloxiprin should prove to be of benefit to people intolerant to other forms of aspirin.

1936 Victoria Road
West Ryde, New South Wales, Australia

- 1434 Bowman, D. & Eadie, M. J. **An evaluation of methysergide in the prevention of migraine and other vascular headaches.** (Letter) *Medical Journal of Australia*, 2(3):118-119, 1963.

A few observations from a small controlled trial of methysergide and a placebo in the interval therapy of classical migraine are presented. There was no statistically significant prophylactic value for methysergide, although it tended to be more effective than both placebo and previous therapy. The dosage used, however, was lower (4 mg/day) than that used in previously described studies that were more successful (6 mg/day). Side effects occurred with both the drug and placebo, the incidence being 24% higher in the drug-treated patients. (This percentage is similar to previous studies.) Methysergide may prove to be useful for migraine if the optimal dosage for each patient is sought.

Brisbane Hospital
Brisbane, Australia

- 1435 Wyant, Gordon M., Cockings, Edward C., & Muir, John M. **Clinical experiences with the azeotropic mixture of halothane and diethyl ether: Report of over 6,000 unselected cases.** *Anesthesia and Analgesia*, 42(2):188-203, 1963.

This is a review of 6,121 administrations of the azeotropic mixture of halothane and diethyl ether over the years 1960 and 1961. The series was entirely unselected except for the omission of patients undergoing open-heart surgery. Twenty-four tables give data relevant to the patients (3,370 females and 2,751 males). The following topics are tabulated: age (a few hours to 103 years); physical status; duration of operation and anesthesia; premedication—meperidine, atropine, scopolamine, Pantopon (the hydrochlorides of the opium alkaloids), antinauseants, tranquilizers, barbiturates, and antihistaminics; site of the operation; principal positions; systems of administration; preoperative therapy—digitalis, quinidine, anticonvulsants, narcotics, barbiturates, tranquilizers, endocrines, etc.; preoperative complications; amount of azeotrope used per 15 minutes anesthesia (< 5 to 30 ml, the majority < 5 ml), occurrence of hypotension; hypotension during induction and during maintenance by age and physical status; hypotension during maintenance by preoperative pathology; treatment of hypotension; postoperative nausea and emesis alone and in

relation to operative hypotension, anesthesia time and operation site, age and physical status, and preoperative complications; and deaths. Case reports are given of the six deaths that occurred in this series in which anesthesia management might have been implicated only in two of them. In comparison with halothane anesthesia alone, the azeotrope is preferable because it has a wider margin of safety, which allows its administration without the benefit of calibrated vaporizers, but with results similar to those from halothane using such vaporizers. It is shown that the azeotrope can be used and has been used safely in all kinds of operations.

University of Saskatchewan
Saskatchewan, Canada

- 1436 Gulie, Leslie A. **Intravenous methylphenidate—A pilot study.** *Medical Journal of Australia*, 2(3):93-97, 1963.

A simple clinical observation was made of the action of methylphenidate on the cardiovascular system, and an assessment was made concerning the drug's safety. The subjects were 20 females (15 to 55 years old) who had recently been admitted to an acute psychiatric hospital. The patients were composed of a group of 8 mute and unresponsive but conscious patients (7 schizophrenic and 1 psychotic depressive) and a group of 12 disturbed neurotics, with anxiety, depression, and difficulty in verbalizing. Each subject received a dose of 20 mg methylphenidate i.v. The physiological phenomena that occurred in a number of cases were moderate increases in systolic blood pressure and in pulse rate. In one patient, there was a violent somatic reaction (screams, muscle tension) that was curtailed by an injection of sodium amylobarbitone i.v. Although no other grave complications were seen, in view of these cardiovascular responses, care should be used when giving the drug to the elderly and to patients with cerebral arteriopathy or with cardiac decompensation. In the psychological findings, there were seven successes and one failure in the psychotic group. In all cases but one, the mute state was dispelled. The effect of the drug in this group was much more dramatic than in the neurotic group. In the neurotic group of tense and anxious women, only one case was a failure, assuming the essential criteria for success as being increased verbalization with diminution of tension.

Mental Hygiene Department
Melbourne, Australia

- 1437** Bhattacharya, A. & West, E. D. **Comparison of salivary suppression by intravenous and subcutaneous atropine before E.C.T.** *British Journal of Psychiatry*, 109(462):631-634, 1963.

This paper reports the comparative effects of i.v. and s.c. atropine in suppressing salivation before giving EST. The subjects were 23 patients who were undergoing EST as inpatients. Saliva was measured by its absorption on three dental rolls left in the patient's mouth for 2 minutes; the rolls were weighed before and after insertion. Readings were taken before and after atropine. Each patient was subjected to both routes of administration. The dose of atropine sulfate used was 0.6 mg (0.01 gr). Salivary estimations were made 10 minutes after i.v. injection and 40 minutes after s.c. injection. No significant difference was found between the two methods of injection. In view of its superior vagal blocking effect and salivary suppression, i.v. atropine is the premedication of choice before EST therapy.

Belmont Hospital
Sutton, Surrey, England

- 1438** Gilman, Sid, MacFadyen, D. J., & Denny-Brown, D. **Decerebrate phenomena after carotid amobarbital injection.** *Archives of Neurology*, 8:662-675, 1963.

This work was done to ascertain whether the paralysis and release symptoms noted after the intracarotid injection of amobarbital could aid further understanding of the nature of spasticity and dystonia, and whether it could provide an objective measure of the activity of subcortical motor mechanisms. The group of patients tested consisted of four chronic alcoholic controls (three males and one female, 41 to 54 years old), six hemiplegics (all males, 60 to 70 years old), six patients with Parkinson's disease (three males and three females, 44 to 69 years old), four patients with Huntington's chorea (two males and two females, 39 to 67 years old), one case of double athetosis (48-year-old female), and one case of olivopontocerebellar atrophy (71-year-old female). The dosage of amobarbital sodium was 200 mg, injected over a period of 4 to 6 seconds. In the controls, the head and eyes deviated to the side of injection, with dystonic flexion and adduction of the contralateral upper limb and clonic extension and adduction of the lower limb lasting 6 to 12 minutes. Powerful clonic hemidecerebrate extension spasm of upper and lower opposite limbs preceded

this posture. In four of the hemiplegic patients, injection opposite the hemiplegia transformed the mildly spastic hemiplegia into an intense hemiplegic dystonia for 5 to 15 minutes, preceded by intense clonic hemidecerebrate extension in two of the patients. In two other hemiplegics who were unchanged by the injection, subsequent arteriography showed carotid occlusion. In the remaining subjects, carotid injection suppressed contralateral involuntary movement and any rigidity for 10 to 30 minutes. Tremor returned later than did willed movements. One choreic and 2 parkinsonians showed mild transient hemidecerebrate postures. A period of flaccidity lasting 10 to 15 minutes was characteristic of all extrapyramidal disorders, indicating extensive disturbance in the function of subcortical structures.

Boston City Hospital
Boston, Massachusetts

- 1439** Burbank, Paul M. **Intravenous Nisentil and Lofran in dental anesthesia: A report on 2,000 cases.** *Anesthesia and Analgesia*, 42(2):275-282, 1963.

This paper presents a method of balanced anesthesia that uses both the i.v. and inhalation routes, and supplemented by local anesthesia. Its use in 2,000 patients (55% female and 45% male, 15 to 84 years old) is surveyed. The technique consists of a combination of four drugs, administered i.v., plus nitrous oxide and oxygen by inhalation, and an occasional supplementation of local anesthesia—2% xylocaine (or lidocaine) hydrochloride. The four drugs given i.v. are these: a synthetic narcotic, Nisentil (α -prodine hydrochloride), 12 to 30 mg; a narcotic antagonist, Lofran (1-allorphan tartrate), in a dosage of 1/50 that of Nisentil; atropine sulfate, 0.432 mg; and a barbiturate, Nembutal (pentobarbital sodium), 25 to 100 mg. This combination of intravenous and inhalation agents has many advantages. It is extremely safe and creates very little, if any, anesthetic insult to the patient. The anesthetic is readily administered, it is extremely pleasant to the patient, the danger of overdosage is remote, and the combination of drugs used yields an effective analgesic, sedative, and hypnotic effect. Of the 2,000 patients in this series, only 50 (2.5%) experienced nausea and only 18 (0.9%) vomited postoperatively. The majority of these was among the small group of patients who received 24 to 30 mg of Nisentil. In the author's opinion, this

technique most nearly approximates the ideal anesthetic for ambulatory oral-surgery patients.

Elmwood Medical Center
Rochester, New York

1440 MacDonald, Ian J. A case of Gilles de la Tourette syndrome, with some aetiological observations. *British Journal of Psychiatry*, 109(459):206-210, 1963.

A case of the rare Gilles de la Tourette syndrome is described that occurred in a girl born on February 28, 1938. This patient is presented because her life history is known in considerable detail, and, although the prognosis seemed extremely poor, she made a complete symptomatic recovery and gained considerably in her personality. Throughout her life she was beset by the symptoms of the syndrome. At the age of 19, she was referred for long-term psychotherapy. The complaints were still of turns, facial tics, and compulsive utterances. The aim of treatment was to engender a feeling of anxiety due to the fear of loss of internal control and, at the same time, enable the patient to test out her view of the psychiatrist as an aggressor. For this purpose, drugs with abreactive properties were used to produce a gradually increasing feeling of disruption. She was given 12 treatments, spaced irregularly, as follows: (1) 7- $\frac{1}{2}$ gr amylobarbitone sodium i.v. (to produce relaxation); (2) 15 mg methylamphetamine i.v. followed by 7- $\frac{1}{2}$ gr amylobarbitone i.v. to counteract the former; (3-5) 30 mg methylamphetamine followed by 7- $\frac{1}{2}$ gr amylobarbitone i.v.; (6) inhalation of carbogen (CO₂); (7-10) 30 mg methylamphetamine i.v. plus inhalation of CO₂; and (11-12) thiopentone sodium i.v. She was discharged after 8 weeks, free of symptoms, and feeling more confidently outgoing and less self-conscious. This improvement has been maintained for 4- $\frac{1}{2}$ years, during which time the patient has become an assistant nurse and has married happily. Certain observations are made at the end of this report about the basal ganglia as the probable site of disturbance in this condition.

St. George's Hospital
London, England

1441 Blom, Sigfrid. Tic douloureux treated with new anticonvulsant. *Archives of Neurology*, 9:285-290, 1963.

The treatment of tic douloureux with a new anticonvulsant, Geigy 32883 [5-carbamyl-di-benz-(b,f)-azepin], an iminostilbene deri-

vative, is reported. A special consideration is given to the effect of the drug in relapse. Forty patients (27 females and 13 males, 26 to 83 years old) were given 200 mg q.i.d. In some patients, this dose was lowered because of secondary effects or raised because of ineffectiveness (highest dose was 200 mg seven times daily). Thirty-six of the 40 patients were relieved of pain attacks within 24 hours, when a sufficient amount of the drug was given. Three of the four who were not relieved by G 32883 alone responded satisfactorily to a combination of G 32883 and diphenylhydantoin (100 mg b.i.d.). Twenty-seven patients have taken G 32883 for six months or more. Twenty-two of these were still without pain after this time, seven of them, however, because of spontaneous remission. Two of the remaining five were free from pain on a combination of G 32883 and diphenylhydantoin. Eleven patients discontinued treatment on their own accord in the belief that they had been cured. All experienced pain again within 24 hours, but the attacks disappeared when treatment was recommended.

Akademiska Sjukhuset
Uppsala, Sweden

1442 Durell, J. & Pollin, W. A trial on chronic schizophrenic patients of oxypertine, a psychotropic drug with an indole ring. *British Journal of Psychiatry*, 109(462):687-691, 1963.

Oxypertine, a compound chemically related to tryptophane by the presence of the indole nucleus, has been administered to a group of 12 chronic schizophrenic men previously studied intensively for several years. Prior to this study, they had been given tryptophane loads. Their ages ranged from 30 to 44 years, and their duration of hospitalization ranged from 7 to 25 years. The study consisted of two phases: (1) In the pilot phase, five men were given increasing dosages of oxypertine (maximum 120 mg/day) for 5 weeks, while the remainder received placebo. (2) In the second phase, all 12 patients were given the drug 1 month after the end of the first phase in increasing dosages up to 120 mg/day; the dosages then were adjusted to each patient (raised or lowered as clinically indicated). The second phase lasted 4 months. The patients were assessed by personal observations, psychiatric interviews, and the V.A. Multi-dimensional Scale for Rating Psychiatric Patients. During the drug period, a third of the patients showed unambiguous significant improvement so that the possibility of

discharge to outpatient status became a realistic goal. Another third of the patients showed some, but less marked, improvement. The pharmacological effects of the drug, which were often dramatic, as well as the changing attitudes of the ward staff seemed to contribute to the overall improvement.

National Institute of Mental Health
Bethesda, Maryland

See also: 1062, 1066, 1072, 1073, 1074,
1075, 1173, 1276, 1278, 1279, 1295

SIDE EFFECTS

1443 Lustig, F. W. A fatal case of hexachlorophane ("pHisoHex") poisoning. Medical Journal of Australia, 1(20):737, 1963.

A mentally retarded 6-year-old girl, hyperactive, restless, emotionally disturbed, and extremely difficult to control, died 9 hours after drinking about 4 to 5 ounces of pHisoHex (2,2"-methylenebis[3,4,6]trichlorophenol). (She had been under treatment for bacillary dysentery, but was free of bowel symptoms.) Gastric lavage was performed within about 15 minutes, but the child quickly became comatose. All efforts to try to arouse her failed. She was slightly cyanosed, with thready pulse and a blood pressure of 90/40 mm Hg; the conjunctival and plantar reflexes were absent, and the light reflex was sluggish. Her breathing failed, she was in a state of peripheral circulatory failure, and she later had a convulsion. Autopsy revealed congestion of the organs and severe inflammation of the stomach, appearances consistent with death from an irritant poison. No reference to the human oral toxicity of this drug or to its major components, hexachlorophane and entsufon, has been recorded. From animal studies, the lethal dose of pHisoHex for a child weighing 36 pounds (as did the patient) is assumed to be 3.5 fluid ounces.

Department of Mental Hygiene
Victoria, Australia

1444 Gold, Norman. Self-intoxication by petrol vapour inhalation. Medical Journal of Australia, 2(14):582-584, 1963.

A general discussion of self-intoxication by gasoline-vapor inhalation is given in the first part of this paper, in which it is noted that the aromatic fraction of gasoline can produce convulsions and tetraethyl lead can poison the CNS. Symptoms of intoxication occur when the concentration reaches one part in a thousand of air. The effect varies according to the quantity of gasoline absorbed. Immediate effects may include headache, drowsiness, a feeling of numbness and dullness, vertigo, tinnitus, ataxia, blurring of vision, anorexia, and nausea.

The symptoms resemble alcohol intoxication with mental confusion. Delirium, with bouts of mania, confusion, and visual hallucinations, have been reported, and gasoline intoxication has been mistaken for schizophrenia. Chronic inhalation can produce muscular cramps, loss of weight, epileptic seizures, or death. The clinical record of a 14-year-old boy who had been sniffing gasoline periodically for a year is described. He had come from a very insecure background. The practice ceased after his father's remarriage and the family resettlement, but it recommenced when he was faced with the stress of school examinations. The literature shows that gasoline is not, however, used widely for self-intoxication. No withdrawal symptoms have been reported. All the patients have come from homes in which there has been a disturbance in their relationship with their parents.

Department of Health Services
Launceston, Australia

1445 McDonald, I. A case of suxamethonium sensitivity. Medical Journal of Australia, 2(6):234-235, 1963.

A healthy 6-year-old boy (48 pounds) experienced a phase-2 block after he was anesthetized through venipuncture when thiopentone (150 mg), pethidine (15 mg), atropine (0.6 mg), and suxamethonium (12 mg) for an appendectomy at 8 P.M. He remained fully paralyzed until about 10 P.M. The patient's condition was good, and he appeared warm and pink; it was apparent, however, that more relaxation than necessary had been obtained. In view of the patient's good condition and the "relaxed" feel of the bag, it was decided to maintain respiration and await events. A spirometer tracing is given of the patterns of breathing, which demonstrate the return of spontaneous respiration at 9:45 P.M. At 10:30 P.M., 0.3 mg atropine was given i.v., and 15 seconds later the patient became cyanosed and pulseless. After three doses of 0.5 mg neostigmine, there was a rapid return of respiration between 10:35 and 11 P.M. A phase-2 block following a single dose of suxamethonium is stated to be a rarity in the writer's experience. Phase-

2 block is a benign condition, however, and catastrophe is more likely to arise during active attempts to reverse the block. The accident with atropine is the writer's first; possibly it was due to hypercarbia.

Prince Henry's Hospital
Melbourne, Australia

1446 Ferriss, Gregory S. & Hackett, Earl R. **Cardiac arrest during intravenous metrazol administration. Report of a case during EEG activation procedure.** *Electroencephalography and Clinical Neurophysiology*, 15(5):892-895, 1963.

During the diagnostic administration of pentylenetetrazol, cardiac arrest was recorded in a 46-year-old male who was admitted for evaluation of peculiar behavior. Laboratory studies, X-rays of the skull, ECG, and the waking, drowsy, and sleep EEG's were normal. In an effort to delineate a possible temporal or frontotemporal focus, pentylenetetrazol activation was performed. The patient had not received any medication for the preceding 7 days. With the patient supine, the drug was given i.v. in 50-mg doses over a 10-second interval every 30 seconds. Sixteen seconds after the seventh injection (total dose 350 mg), there was a very pronounced bradycardia and irregularities of rhythm. The drug was discontinued. ECG monitoring of the heart showed the mechanism to be a sinus arrest. This was then followed by an A-V nodal bradycardia. EEG abnormalities were compatible with ischemic anoxia. A review of 33 other records of pentylenetetrazol activation demonstrated bradycardia in 2, tachycardia in 18, and no change in heart rate in 13.

Louisiana State University, School of Medicine
New Orleans, Louisiana

1447 Collins, Ian S. **Some side effects of thioridazine.** (Letter) *Medical Journal of Australia*, 2(23):971, 1963.

This letter is a rebuttal to a previous communication (November 16, 1963 issue) in which the author reported amenorrhea and related disorders in patients taking thioridazine, as well as the occurrence of two miscarriages in one woman on the drug. The present author states that amenorrhea has been shown to result from a multiplicity of varied and unrelated kinds of tranquilizers. He cites many cases from the literature to substantiate his arguments. With regard to

the patient who miscarried twice, he states that thioridazine was tested in pregnant animals and was found to be free of teratogenic activity. It has also been used clinically during pregnancy, and no ill effects have been noted. The writer feels that much more evidence is required before attributing this phenomenon to the effects of thioridazine.

Sandoz Australia Pty., Ltd.
Ultimo, New South Wales, Australia

1448 Cohen, P. H. **Some side effects of thioridazine.** (Letter) *Medical Journal of Australia*, 2(20):864-865, 1963.

In view of the recent addition of thioridazine to the National Health Service formulary (Australia), the author reports some side effects observed in his patients on the drug. The first is complete amenorrhea, which occurred in 25% of menstrual-age females taking doses of 50 to 300 mg/day. Also noted were oligomenorrhea and irregular oropharyngeal blood spotting. A more serious effect, which occurred in one patient (a 32-year-old mother of two healthy children), was fetal death in utero during the fourth month in two pregnancies. The woman had been taking 100 to 300 mg/day for 18 months. Although conclusions cannot be drawn from this one incidence, care should be used when prescribing this drug to patients in whom there is a possibility of pregnancy.

Clarendon Clinic
East Melbourne, Australia

1449 Willis, E. J. **Sulthiame ("Ospolot") in the treatment of temporal lobe epilepsy.** (Letter) *Medical Journal of Australia*, 2(20):865-866, 1963.

A communication in the June 29, 1963 issue reported that a child experienced hyperpnea while under sulthiame therapy. Some workers have attributed the reaction to the impaired function of the tempororhinencephalon and diencephalon. The author states that a sulthiame tablet of smaller strength, 50 mg, has recently been introduced to provide greater flexibility of dosage.

FBA Pharmaceuticals (Australia) Pty., Ltd.
Botany, New South Wales, Australia

SIDE EFFECTS 1450-1453

- 1450 Lahz, John. **Self-intoxication by petrol vapour inhalation.** (Letter) Medical Journal of Australia, 2(19):811, 1963.

In view of a report of self-intoxication induced by gasoline vapor, in which it was stated that this habit can be indicative of a psychiatric upset, the author of this letter states that as a child (4 to 5 years old) he also like to sniff gasoline. On one occasion he lost consciousness, but he regained it a few hours later and had no aftereffects. Thereafter, he naturally lost any desire to continue with this pastime. In conclusion, however, the author states that he feels this childhood habit was not due to any psychosis, but just because he liked the smell of gasoline.

Wickham Terrace
Brisbane, Australia

- 1451 Refshauge, W. D. **A danger of tranlylcypromine.** (Letter) Medical Journal of Australia, 2(17):730-731, 1963.

In this letter from the Director-General of Health (Australia), he states that he has been advised by Smith Kline and French Laboratories, Ltd., and by recent reports in the British Medical Journal and The Lancet of the occurrence of intracranial bleeding in patients receiving tranlylcypromine. The manufacturer advised that the prescribing information has pointed out that the drug occasionally affects blood pressure, usually in the form of a transient hypotensive reaction, and that hypertension and severe headache may also be encountered. The manufacturer has tried to notify all doctors in Australia and New Zealand of these circumstances by a letter, which also provides details of a possible explanation of the reaction, a description of the drug's side effects, and the possible association of cheese-eating with a hypertensive reaction. Also enclosed in the letter is the most up-to-date prescribing information, which should be read carefully with reference to treatment, side effects, and contraindications.

Department of Health
Canberra, Australia

- 1452 Morris, Robert B. **Sulthiame ("Ospolot") in the treatment of temporal lobe epilepsy.** (Letter) Medical Journal of Australia, 2(16):684-685, 1963.

A case report is given of the development of hyperpnea in a 3-year-old boy being treated with sulthiame. The boy had a

series of akinetic episodes over a period of 2 weeks. He was given $\frac{1}{4}$ gr phenobarbital t.i.d., and no further episodes were noted for 6 months. Convulsions followed that were frequent and composed of four distinct types: grand mal, myoclonic, akinetic (drop), and episodes of a dreamy state lasting 2 or 3 minutes. For 4 weeks he was given various combinations and dosages of prominal, diphenylhydantoin, and promidone, but they were ineffective. Sulthiame was then added to the three drugs in a dosage of 100 mg/day for 1 week and of 100 mg t.i.d. thereafter. The convulsions ceased, but hyperpnea developed and gradually grew more marked. Blood studies were normal, and there was no cough nor were there cardiovascular and respiratory signs. The dosage of sulthiame was reduced, but hyperpnea persisted. The drug was eventually stopped, and the patient's breathing finally returned to normal. He was probably sensitive to sulthiame, and hyperpnea followed a disturbance of electrolytes caused by this drug.

43A Watt Street
Newcastle, Australia

- 1453 Phelan, P. D. **Accidental poisoning in childhood.** Medical Journal of Australia, 2(16):656-657, 1963.

This survey is a retrospective study of admissions to the Brisbane Children's Hospital, in the 5- $\frac{1}{2}$ -year period from July 1957 to December 1962, of children (up to 11 years old) who had accidentally ingested some chemical substance. Accidental poisoning is a frequent reason for admission, as shown by the numbers of admissions tabulated for each year; it rarely, however, causes serious medical problems. Those children who develop serious complications usually show some evidence of this soon after their arrival at the hospital. In the majority of cases, children who have ingested poisons simply require observation, and are for this purpose. Tables are included of the age and sex of the children admitted by year; the types of substances ingested, such as hydrocarbons, medicines (barbiturates, aspirin, laxatives, and antihistamines), and insecticides; and the incidence of pneumonitis after the ingestion of various hydrocarbons. A graph shows the admissions per month of children who had ingested the main groups of chemical substances. Kerosene was the agent in 31% of the 805 cases surveyed.

Brisbane Children's Hospital
Brisbane, Australia

- 1454 Hopkins, Paul. The effect of "Ancolan" and other drugs in early pregnancy. (Letter) Medical Journal of Australia, 1(9):330, 1963.

The author, having previously reported his results with the use of meclizine (Ancolan) and Ancoloxin in early pregnancy, reports results with three drugs administered less frequently. Trifluoperazine was used in 17 cases, and all 17 babies were normal; Maredox was used in 14 cases, and 13 babies were normal (the abnormal baby had duodenal atresia, and the mother also had taken meclizine); and dicyclomine hydrochloride (Dibendox) was used in six cases, and all six babies were normal.

Gordon Street
Mackay, Queensland, Australia

- 1455 Hopkins, Paul & Robertson, Duncan. The effect of "Ancolan" and other drugs in early pregnancy. (Letter) Medical Journal of Australia, 1(9):329-330, 1963.

In response to a previous letter warning of the dangers of using meclizine or a meclizine--pyridoxine combination in early pregnancy, the present authors made a survey of 200 patients who had taken either treatment during the period May 1957 to December 1962. Of these, 125 received meclozine and 75 the combination, and 187 had normal, healthy children. Eight babies were stillborn because of revealed and concealed accidental hemorrhage (1), maternal toxemia (1), birth injury (3), cord wrapped tightly around the neck (1), and no cause or placental insufficiency (2). Five babies had some abnormality, but all five are still alive. The abnormalities were hydrocephalus, duodenal atresia, mild talipes of the right foot, mongolism, or webbing of some fingers and toes. From these data, it appears to the authors that meclizine and the meclizine--pyridoxine combination are quite safe to give to pregnant women.

Gordon Street
Mackay, Queensland

- 1456 Digiovanni, Anthony J. Xylacaine convulsions: Analysis of two cases intoxication or sensitization? Anesthesia and Analgesia, 42(3):355-359, 1963.

Two young male patients who were subjected to daily stellate ganglion blocks exhibited generalized convulsive movements with sub-toxic dosages of diethylamine-2,6-aceto-

xylidide (lidocaine). An average of 8.0 ml of 2% lidocaine with epinephrine 1:80,000, without preanesthetic medication, was used for daily injection in an attempt to salvage the gangrenous finger of a 19-year-old white male, 70 inches in height and weighing 165 pounds. On the fifth day after 0.5 ml of the drug had been injected, he sustained progressive convulsive movements with an increase in pulse rate; cool, moist skin; emesis; and retention of consciousness. An intradermal injection of the solution produced no reaction either locally or systemically. On the following day, an injection of 4.0 normal saline produced no effect, so lidocaine was injected slowly, with frequent aspirations for blood. After 50 ml had been given, he sustained the same effects as on the previous day. A 20-year-old white male, 68 inches in height and weighing 140 pounds, with an almost completely amputated little finger was given 30 ml of 1.5% lidocaine with epinephrine 1:120,000 for anesthesia. On the third day after 1.0 ml of 2% lidocaine with 1:80,000 epinephrine had been injected, the patient became unresponsive and exhibited generalized clonic convulsion. This condition persisted for 60 to 90 minutes until sodium thiopentone could be given. The ganglion blocks were continued 4 days following the convulsion, using 8.0 ml of 0.15% tetracaine with epinephrine 1:100,000. This was repeated 2 days later; there were no complications. Direct evidence for the formulation of a definite conclusion as to whether the adverse reaction was due to drug intoxication or sensitization is lacking. However, the author is inclined to favor the idea of sensitization.

USAF Hospital Eglin
Eglin Air Force Base, Florida

- 1457 Davis, John D. & Miller, Neal E. Fear and pain: Their effect on self-injection of amobarbital sodium by rats. Science, 141(3587):1286-1287, 1963.

Twenty-eight male albino rats, weighing approximately 330 g, were run in yoked pairs in adjoining Skinner boxes. One rat in each pair served as a control. The rats received occasional brief electric shocks when they pressed a bar, which caused them to be injected with approximately 1.5 mg/kg amobarbital sodium. The control rats were injected when their partners pressed the bar; their own bars activated a recorder. Each pair of rats was run for 1 hour each day. The author concludes that for the shocked rats, the injections had a reinforcing effect that caused learning through the third

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day, but the injections did not have any appreciable reinforcing effect for animals run without shock.

Yale University
New Haven, Connecticut

1458 Rupe, Billy D., Bousquet, William F., & Miya, Tom S. **Stress modification of drug response.** *Science*, 141(3586):1186-1187, 1963.

Male Holtzman rats were stressed by unilateral hind-leg ligation for 2.5 hours, at which time, depletion of ascorbic acid in the adrenals was at a maximum. Hexobarbital (100 mg/kg), or meprobamate (300 mg/kg), or pentobarbital (35 mg/kg), or barbital (250 mg/kg) was administered by i.p. injection to groups of stressed and control rats. The stressed animals showed a significantly decreased pharmacological response to the effects of hexobarbital, meprobamate, and pentobarbital. This effect is dependent upon an intact pituitary--adrenal axis, since it is absent in both hypophysectomized and adrenalectomized animals. The effect can, however, be simulated by i.v. administration of adrenocorticotrophic hormone or corticosterone. The effect of stress on drug response is not noted with barbital, a compound which is not metabolized; this effect is inhibited by treatment of the animal with a drug metabolism inhibitor such as SKF-525A (diethylaminoethyl 2,2-diphenylpentanoate). Compounds that can stimulate adrenocorticotrophic hormone secretion or act directly on the adrenals to produce corticosteroids should thus be able to stimulate their own metabolism or that of other drugs.

Purdue University
Lafayette, Indiana

1459 Knight, W. Rea, Holtz, John R., & Sprogis, George R. **Acetophenazine and fighting behavior in mice.** *Science*, 141(3583):830-831, 1963.

Acetophenazine, a phenothiazine known to reduce fear, was tested for ability to facilitate fighting in mature mice. Sixty-four male C57BL mice were caged in such a way so that no subject could see another mouse. When the mice were 10 to 12 weeks old they were randomly paired and assigned to either the drug or control group. On the fourth day, experimental pairs received 2.4 mg/kg of acetophenazine, and control pairs received saline. Drugged pairs did not differ

significantly from controls in fighting latency; however, the time lapse from the first fight to submission was significantly longer for drugged pairs. The neural mechanisms of aggressive behavior and the observation that acetophenazine prolongs fighting brings one to suspect that an important subcortical locus of the drug's activity might be the septal region or Hess's "flight" center in the hypothalamus, or both.

Hiram College
Hiram, Ohio

1460 Fraňková, S. **Vliv Benactyzinu a LSD na vyšší nervovou činnost krys.** (The effect of benactyzine and LSD on the higher nervous activity in rats.) *Activitas Nervosa Superior*, 5:214-215, 1963.

A study was made of the effects of benactyzine and LSD on orienting activity and spontaneous motor activity in rats. When given 10 mg/kg benactyzine i.p., eight rats classed as having constitutionally low sensitivity showed a remarkable increase, and eight rats with relatively high sensitivity showed a moderate increase in erection reactions. A decrease in immobility was observed in both groups. Control rats were given isotonic saline solution i.p. A dose of 40 mg/kg depressed the elevated level of activity in rats of both groups. In doses of 0.05 mg/kg, LSD depressed motor activity in both groups and increased defecation. Increasing the LSD dosage to 0.1 mg/kg further increased the damping effect on activity.

Human Nutrition Research Institute
Prague, Czechoslovakia

1461 Woolley, D. W. & van der Hoeven, Th. **Alteration in learning ability caused by changes in cerebral serotonin and catechol amines.** *Science*, 139(3555):610-611, 1963.

The relationship of changes in levels of serotonin and catecholamines to changes in learning ability was studied in mice. To measure learning ability of mice, a simple T-shaped maze was used with a transparent top so that the mouse always saw the observer. The mouse was placed at the bottom of the stem of the T and given exactly 2 minutes to explore the maze, and to learn that a reward was obtained only by making the correct turn at the union of the stem with the crossarms. The mouse was then tested in 10 tries to determine how well it

had learned its lesson. The average scores for 6 groups of 10 mice each were 7.5, 7.1, 7.8, 7.3, 7.1, 7.5; standard deviation ± 0.2 ; standard error, ± 0.1 . Increases in brain serotonin alone were induced with 5HTP plus 1-benzyl-2-methyl-5-methoxytryptamine (BAS). Total-body serotonin was increased with 5HTP alone. Catecholamines were increased by injecting DOPA. Both serotonin and catecholamines were increased with iproniazid. Increases in cerebral serotonin, or serotonin plus catecholamines resulted in decreases in learning ability. Decreases of serotonin and catecholamines increased the learning ability.

Rockefeller Institute
New York 21, New York

- 1462 Gresham, Samuel C., Webb, Wilse B., & Williams, Robert L. **Alcohol and caffeine: Effect on inferred visual dreaming.** Science, 140(3572):1226-1227, 1963.

To test the hypothesis that alcohol would decrease, and caffeine increase, EEG stage 1—rapid-eye-movement (REM) time and inferred dreaming, seven medical students, 23 to 28 years of age, were continuously monitored by EEG and electrooculographic recording while sleeping. Recordings were made on 2 baseline nights, 1 drug night, another baseline night, and a second drug night, in that order, with 4 hours of extra-laboratory sleep interposed between the first drug night and the fourth baseline night. On the drug nights, each subject drank 1 g/kg 95% ethyl alcohol or 0.005 g/kg caffeine citrate mixed with 400 ml of orange juice. On baseline nights, only orange juice was drunk. This amount of alcohol taken at bed time reduced the total duration of stage 1 EEG—REM time and inferred dreaming in the first 5 hours of sleep. The caffeine had no significant effect on these parameters of sleep.

University of Florida College of Medicine
Gainesville, Florida

- 1463 Whalen, Richard E. & Nadler, Ronald D. **Suppression of the development of female mating behavior by estrogen administered in infancy.** Science, 141(3577):273-274, 1963.

Fourteen female rats were injected s.c. with 200 μ g of estradiol benzoate in 0.2 ml of mineral oil on the fourth day after birth. Five control female rats were given 0.2 ml of mineral oil. At 95 days of age, they

were ovariectomized and caged in pairs. Mating tests were begun at approximately 130 days of age. Subjects were given 50 μ g of estradiol benzoate at 72 hours and 25 μ g of estradiol benzoate at 48 hours prior to each set of mating tests. Five hours before testing they were given 1.0 mg of progesterone. Each subject was tested twice for a 15-minute period, with an intertest interval of 14 days. When mounted by males, the estrogen-treated females did not show lordosis; instead, on 40% of the mounts the female responded by kicking the male. Low intromission and ejaculation frequencies were observed among treated females. Control females assumed the lordosis posture when mounted and permitted intromission and ejaculation. Thus, estrogen treatment at the appropriate dose level during the neonatal period acts to reduce sexual responsiveness in females, which is normally induced by estrogen and progesterone.

University of California
Los Angeles, California

- 1464 Cook, Leonard, Davidson, Arnold B., Davis, Dixon J., Green, Harry, & Fellows, Edwin J. **Ribonucleic acid: Effect on conditioned behavior in rats.** Science, 141(3577):268-269, 1963.

The relationship between chronic treatment with purified RNA to changes in acquisition and extinction of a conditioned response was studied in rats. Sprague--Dawley rats, 150 to 200 g in weight, were divided by weight into two groups of eight. One group was injected i.p. daily with 160 mg/kg RNA, and the other group was injected with normal saline. Over a period of more than 10 weeks, no significant differences were noted, except for a slightly lower rate of weight gain in the treated group. After 53 days, the rats were individually placed in the same position in a chamber with an electrified grid floor, a pole suspended from the top center, and a buzzer. In unconditioned response trials, the buzzer and electric shock through the grid floor were presented simultaneously; in conditioned response trials, only the buzzer was presented. Each trial was terminated by a response (jumping onto the pole after onset of stimuli) or at the end of 30 seconds. In the treated group, the rate of acquisition of the response was markedly faster than in the controls. Resistance to extinction was higher in the treated rats than in controls after 3 days, 1 week, 2 weeks, or 1 month of daily treatment.

Smith, Kline, and French Laboratories
Philadelphia, Pennsylvania

- 1465 Hingtgen, J. N. & Aprison, M. H. **Behavioral response rates in pigeons: Effect of α -methyl-m-tyrosine.** *Science*, 141(3576):169-171, 1963.

As part of a study to correlate changes in serotonin level with changes in behavior, 100 mg/kg α -methyl-m-tyrosine, i.m., which differentially depletes serotonin and norepinephrine in both brain and heart, was given to two groups of pigeons trained to peck at a key for food. The first group received an injection 12 hours before the daily session and showed no behavioral effect. Response rates of birds in the second group, which were injected 30 minutes after the start of the daily session, decreased and returned to normal within 9 hours after injection. Preliminary data on brain serotonin of pigeons indicate that the disruption of behavior follows the same time course as the change in serotonin.

Indiana University Medical Center
Indianapolis, Indiana

- 1466 Bourgault, Priscilla C., Karczmar, Alexander G., & Scudder, Charles L. **Contrasting behavioral, pharmacological, neurophysiological, and biochemical profiles of C57 B1/6 and SC-I strains of mice.** *Life Sciences*, 2(8):533-553, 1963.

Preliminary results of a study of the relationship of behavioral, pharmacological, neurophysiological, and biochemical characteristics in C57 B1/6 and SC-I strains of mice are presented. The following procedures were used in the differentiation of the strains: (1) motor activity tests (jiggle cages, Bastian cages, climbing-screen apparatus); (2) measurements of avoidance latency; (3) tests for aggression; (4) electroshock-convulsion latency determinations; (5) pentylenetetrazol responses; (6) adrenal weights; and (7) bioamine assay. Differences in drug sensitivity were tested with the following drugs: chlorpromazine HCl, phenobarbital sodium, reserpine, and pentylenetetrazol. The C57 B1/6 strain was more active and more cautious in its behavior than the SC-I strain. The C57 B1/6 mice were more sensitive to chlorpromazine, reserpine, phenobarbital, and probably, to pentylenetetrazol than were the SC-I mice. Drug sensitivity correlated in these mice with increased motor activity. It was concluded that differences in behavior may be correlated with differential responses to centrally acting agents and with neurophysiological and biochemical characteristics.

Loyola University
Chicago, Illinois

- 1467 Sung, J. H., Marcus, E. M., Purpura, D. P., & Wolf, A. **Behavioral and electroencephalographic responses to gamma aminobutyric acid and histological changes of brain following X-irradiation of head of rabbits.** *Journal of Neuropathology and Experimental Neurology*, 22(2):347-348, 1963.

Since it is known that doses of 50 to 100 mg/kg GABA i.v. do not penetrate the blood-brain barrier in sufficient quantities to produce changes in electrocortical activity, but do produce profound depressant effects on excitatory synaptic activities in cortical regions of blood-brain barrier destruction, this information was used to determine whether the behavioral or electrographic effects of GABA might facilitate correlation of functional and histological changes in the blood-brain barrier after X-irradiation of the head in rabbits. Thirty-four adult male rabbits were used; 21 were irradiated and 13 served as controls. The GABA was given in doses of 65 mg/kg i.v. In unirradiated animals, this dosage of GABA produced chewing, but did not produce significant electrographic changes. Following irradiation, responses to GABA were markedly enhanced. Animals exhibited chewing, head shaking, opisthotonic posture, and ataxia; spontaneous electrocortical activity was depressed. The marked effects of systemic GABA following irradiation of the head indicate an alteration in the function of the blood-brain barrier, which normally is responsible for impeding the passage of GABA from the bloodstream to the surface neurons.

New York, New York

- 1468 Wilber, Charles G. & Burke, J. A. **The effect of lysergic acid diethylamide on swimming time in albino mice.** *Life Sciences*, 2(2):134-138, 1963.

To evaluate the effect of LSD-25 on physical factors in animals, as contrasted with behavioral characteristics, LSD-treated albino mice were forced to swim under controlled conditions. Doses varied from zero (saline controls) to 100 μ g/mouse. Bath temperatures were 7.5°, 10°, 15°, 24°, and 35° C. Some mice swam singly, others in groups of four to determine the effects of crowding. In a 24° C bath, low doses (10 μ g/mouse) of LSD resulted in increased swimming time. Doses above 10 μ g/mouse decreased swimming time. The stimulating effect of LSD at low doses was readily obscured by lowered water temperature and, to some extent, by crowding.

Kent State University
Kent, Ohio

- 1469 Poschel, B. P. H. & Ninteman, F. W.
Norepinephrine: A possible excitatory neurohormone of the reward system. *Life Sciences*, 2(10):782-788, 1963.

Evidence is presented that norepinephrine serves as an excitatory agent in the reward or reinforcement functions of behavior. Three albino, male, adult rats with platinum electrodes implanted in the lateral hypothalamus were trained to press a lever to stimulate their brains electrically. The rats were then injected with tranlycypromine (an MAO inhibitor) and α -methyl-m-tyrosine, which releases brain norepinephrine and dopamine, but not serotonin. A sustained high level of free norepinephrine was thereby made available to central reactive sites. Self-stimulation behavior was greatly enhanced. To show that the increased self-stimulation was not specific to α -methyl-m-tyrosine, tranlycypromine-pretreated rats were given tetrabenazine, which is known to release norepinephrine and serotonin, but not dopamine. Self-stimulatory behavior increased sharply in this test also. Norepinephrine, therefore, seems to exert excitatory effects on the reward system.

Parke, Davis & Company
 Ann Arbor, Michigan

- 1470 Hinton, J. M. **A comparison of the effects of six barbiturates and a placebo on insomnia and motility in psychiatric patients.** *British Journal of Pharmacology and Chemotherapy*, 20(2):319-325, 1963.

Six barbiturates, chosen from each of the three traditional divisions of barbiturates (short-, intermediate-, and long-acting), were tested in a double-blind trial in 24 psychiatric patients with insomnia for duration and depth of effect. Cyclobarbitone, hexobarbitone, and quinalbarbitone were selected from the short-acting barbiturates, pentobarbitone sodium from the intermediate-acting barbiturates, and phenobarbitone sodium from the long-acting barbiturates. Nealbarbitone, an effective sedative with little hypnotic action, was also tested. Each drug was given in its commonly used effective dose and compared with placebo. Each of the barbiturates significantly prolonged sleep and hastened its onset. They also reduced the patients' motility, as recorded by an electronic apparatus attached to the bed. There was no clear difference between these barbiturates in onset and duration of action during the 8 hours of recording; some effect upon sleep or motility was present throughout this period. Differ-

ences between compounds were of degree rather than of duration of action. Pentobarbitone, quinalbarbitone and phenobarbitone were most effective; cyclobarbitone and hexobarbitone were less effective; nealbarbitone had only a weak hypnotic action.

Middlesex Hospital
 London, W.1, England

- 1471 Dandiya, P. C. & Menon, M. K. **Effects of asarone and β -asarone on conditioned responses, fighting behaviour and convulsions.** *British Journal of Pharmacology and Chemotherapy*, 20(3):436-442, 1963.

The influence of asarone and β -asarone (the trans and cis forms of 2,4,5-trimethoxy-1-propenyl benzene), two active principles of the Indian plant *Acorus calamus*, when given alone and together with either reserpine or chlorpromazine, has been studied on the conditioned avoidance response of trained rats, on the fighting behavior of paired mice subjected to mild foot shock, and on electroconvulsions in rats. Except for electroconvulsions, asarone in small doses potentiates the effects of reserpine and of chlorpromazine; β -asarone has no such effect. Estimation of the 5HT content of rat brain showed that neither acorus oil nor its active principles increase the concentration of 5HT, nor do these compounds cause an additional decrease in the 5HT content of the brains of animals treated with reserpine. It is concluded that the potentiating effect of these principles is unrelated to 5HT concentration. In experiments using electroconvulsions, asarone increased the percentage mortality of animals treated with chlorpromazine, but not of those treated with reserpine.

S.M.S. Medical College
 Jaipur, India

- 1472 Domino, Edward F., Corssen, Guenter, & Sweet, Robert B. **Effects of various general anesthetics on the visually evoked response in man.** *Anesthesia and Analgesia*, 42(6):735-747, 1963.

A study was made of the effects of various general anesthetic agents on the visually evoked response (VER) in man. In 50 patients, the VER to flashing light was recorded by electronic averaging techniques at theinion before and during general anesthesia. Preanesthetic medication consisted of i.v. administration of one of the muscarinic blocking agents, 1-hyoscyamine,

atropine, or scopolamine. The data collected with the patients' eyes closed are emphasized, inasmuch as the responses were simpler, larger, and easier to interpret, as compared to eyes open. Cyclopropane and diethyl ether-oxygen were especially effective in markedly altering and depressing the average VER at various planes of surgical anesthesia. Thiamylal sodium i.v. also was capable of maximally depressing the VER, but only in relatively high doses, resulting in marked flattening and burst suppression patterns in the EEG. In contrast, anesthesia produced with nitrous oxide, halothane, and methoxyflurane in oxygen did not significantly obliterate the VER and, in fact, enhanced certain portions of it. The well-known cardiovascular depressant action of halothane and methoxyflurane prohibited deepening of anesthesia to the point where the VER might have been obliterated. All of the anesthetics studied appeared to enhance the late secondary positive wave 4 at critical intermediate depths of surgical anesthesia. Light surgical anesthesia produced an amazing lack of depression of visual input as recorded at the cerebral cortex via scalp leads, although the wave forms were altered and their latencies were prolonged.

University of Michigan Medical Center
Ann Arbor, Michigan

- 1473 Utley, John D. **The effects of anthranilic hydroxamic acid on rat behaviour and rat brain γ -aminobutyric acid, norepinephrine and 5-hydroxytryptamine concentrations.** *Journal of Neurochemistry*, 10 (5):423-432, 1963.

The effects of anthranilic hydroxamic acid (AHA) on rat-brain levels of GABA, norepinephrine (NE), and 5HT, on the EEG, and on glutamate decarboxylase activity were examined in an attempt to correlate observed behavioral changes with these parameters. The AHA (1.0 mg/g) causes depression for 10 hours in rats; half the dose causes tranquilization, as defined by suppression of the conditioned avoidance reaction. Daily injections of 0.5 mg/g causes convulsions on the third day. A correlation between the level of the bound form of brain GABA and seizures is suggested. Both seizures and GABA depletion are reversed by i.v. injected pyridoxal. The AHA inhibits glutamate decarboxylase in vitro and in vivo. In doses of 1.0 mg/g, AHA causes a 90% reduction in brain concentration of NE in rats 3 hours after injection of the drug. The concentration of NE returns to the control value by the sixth hour. The NE drops to 80% of the control level if 0.5 mg/g of AHA is given,

and 73% during seizures. No correlation can be made between brain NE concentration and behavior. The AHA causes no significant alteration in 5HT concentration in rat brain and no change in the rat EEG. When incubated aerobically or anaerobically with rat liver, brain, or plasma, AHA is not hydrolyzed, although the compound disappears from the brain and liver of living rats in 3 hours.

Duke University Medical Center
Durham, North Carolina

- 1474 Collier, H. O. J. & Lee, I. R. **Nociceptive responses of guinea-pigs to intradermal injections of bradykinin and kallidin-10.** *British Journal of Pharmacology and Chemotherapy*, 21(1):155-164, 1963.

The response of guinea pigs to intradermal injection of drugs and strongly anisotonic solutions known to cause pain in human skin was observed, to determine whether the solutions would also cause pain in the test animals, and, if so, whether a method could be devised to measure this effect, in order to predict from animal experiments the likelihood that new substances would either cause or reduce pain in man. The following substances were injected: bradykinin, the decapeptide kallidin-10 acetylcholine bromide, histamine acid phosphate, and 5HT creatinine sulfate. Doses were successively varied by a factor of 10. Nine behavioral responses were observed to follow, with reasonable frequency, intradermal injection of the strongly anisotonic solutions. These responses were recorded on a form, and a procedure was devised for obtaining a nociceptive score from the records. Intradermal injection of bradykinin or kallidin-10 gave a response pattern indistinguishable from that to a strongly anisotonic solution. Each kinin raised the nociceptive score in response to the control solutions, as did acetylcholine and histamine; 5HT and pH changes within the range of 3.1 to 10.3 did not significantly raise the control score. The effect of bradykinin was depressed by s.c. injection of morphine or codeine, but was unaffected by amidopyrine, calcium acetylsalicylate, chlorpromazine, or phenylbutazone.

Park, Davis & Co.
Hounslow, Middlesex, England

See also: 1061, 1067, 1068, 1070, 1077, 1092, 1096, 1097, 1098, 1100, 1101, 1102, 1119, 1120, 1122, 1123, 1179, 1203, 1207

BEHAVIORAL STUDIES

1475 Løvtrup, Søren. A comparative study of the influence of chlorpromazine and imipramine on mitochondrial activity: Oxidation and phosphorylation. *Journal of Neurochemistry*, 10(5):471-477, 1963.

Rat-liver mitochondria were prepared in 0.25 M sucrose and centrifuged. To the main chamber in Warburg vessels was added potassium chloride, magnesium sulfate, potassium phosphate buffer, adenosine triphosphate, 0.1 ml of 0.26 M substrate (with pyruvate an extra 0.1 ml of 10 mM malate was added), and 0.5 ml mitochondria in sucrose solution, corresponding to 0.5 g brain mitochondria or 0.25 g liver mitochondria. Sucrose was added to make the total volume 2 ml. Glucose and hexokinase were placed in the sidearm. Potassium hydroxide on filter paper was added in the center well. The equilibration time was 10 minutes, duration of experiments was 15 to 20 minutes, and incubation temperature was 37°C. Ten experiments were run, two on each of the five substrates: pyruvate (+ malate), succinate, glutamate, α -oxoglutarate, and oxalacetate. Both chlorpromazine and imipramine exerted strong inhibitory action on oxygen uptake and phosphorylation, chlorpromazine being twice as active on a molar basis. Chlorpromazine is a slightly stronger inhibitor of oxidation by both kinds of mitochondria at low concentrations. The effects on phosphorylation are similar, but chlorpromazine does not stimulate phosphorylation at low concentrations. Apparently no uncoupling occurs in the range of strong inhibition. In both oxygen consumption and phosphorylation, no conspicuous tissue specificity could be observed. The inhibitory action was found to be independent of substrate oxidation. The inhibition of oxidation by brain mitochondria for both chlorpromazine and imipramine could not be relieved by 2,4-dinitrophenol.

Institute of Neurobiology,
University of Göteborg
Göteborg, Sweden

1476 Fletscher, A., Burkard, W. P., Burdener, H., & Gey, K. F. Decrease of cerebral 5-hydroxytryptamine and 5-hydroxyindolacetic acid by an arylalkylamine. *Life Sciences*, 2(11):828-833, 1963.

Injection (i.p. or s.c.) of 5 to 25 mg/kg dl-p-chloro-N-methylamphetamine (RO 4-6861) in rats weighing 60 to 90 g causes a progressive diminution of cerebral 5-HT and 5HIAA. Both indolyl compounds were diminished to 30% to 40% of control rats after 16 hours by 25 mg/kg RO 4-6861. Cerebral nor-epinephrine was only slightly diminished (to 90% of controls after 16 hours) by 25 mg/kg RO 4-6861. During the first hours after injection of 25 mg/kg of the drug, the rats show motor excitation, which then gradually diminishes. The drug does not inhibit cerebral decarboxylase or monoamine oxidase in vivo to any considerable extent. The author concludes that RO 4-6861 either inhibits the 5-hydroxylation of tryptophan or promotes the metabolism of stored 5HT through a pathway not leading to 5HIAA.

F. Hoffmann-LaRoche & Co. Ltd.
Basle, Switzerland

1477 Farrant, J. Interactions between cocaine, tyramine and noradrenaline at the noradrenaline store. *British Journal of Pharmacology and Chemotherapy*, 20(3):540-549, 1963.

Cats weighing 1 to 3 kg of either sex were made spinal and others were anesthetized with chloralose and sodium pentobarbitone. Single injections of noradrenaline (2 µg) or adrenaline (5 µg) were administered through the femoral vein. Infusions were given through the other femoral vein. The pressor actions of noradrenaline and of adrenaline were generally decreased except in the case of adrenaline injection in spinal cats during the lowest rate of noradrenaline infusion. The pressor action of tyramine (200 µg) was increased during infusions of either adrenaline or noradrenaline. After an infusion of noradrenaline, the increase in response was prevented by cocaine, methylphenidate, and pipradrol. Pipradrol increased the responses to catecholamines.

Cocaine did not prevent the increase in the noradrenaline content of cat kidney and uterus after an infusion of noradrenaline. Rats weighing 180 to 200 g were pithed and artificially ventilated by a pump. Injections were made into the left femoral vein. The pressor response to noradrenaline (10 µg) was increased by cocaine but the response to tyramine (5 µg) was decreased. Reserpine (5 mg/kg i.p.) prevented the effect of cocaine on the response to tyramine but did not affect the response to noradrenaline. Prolonged treatment with cocaine did not lower the tissue noradrenaline levels nor prevent noradrenaline depletion by reserpine. Interactions between cocaine, tyramine, and noradrenaline may occur at the point where noradrenaline enters its tissue store.

National Institute for Medical Research
Mill Hill, London, N.W.7, England

- 1478 Gokhale, S. C., Gulati, O. D., & Kelkar, V. V. Mechanism of the initial adrenergic effects of bretylium and guanethidine. *British Journal of Pharmacology and Chemotherapy*, 20(2):362-377, 1963.

Eighty-one cats of either sex weighing 2.5 to 4.0 kg were divided into two groups. One group was anesthetized by i.v. injection of 80 mg/kg of chloralose, and the other group (spinal cats) was given only ether anesthesia. Blood pressure, contractions of the nictitating membrane, and contractile force of the exposed heart were recorded. Strips of stomach were obtained from the fundus of rats treated with reserpine. The strips were suspended in a continuous stream of blood pumped from the carotid artery of an anesthetized cat. Bretylium and guanethidine when given (i.v.) to anesthetized and spinal cats increased blood pressure, caused contraction of the nictitating membrane, and increased the cardiac contractile force, all of which were prevented by treatment with phenoxybenzamine and dichloroisoprenaline. Cocaine, imipramine, or reserpine reduced the sensitivity of the spinal cat to bretylium and guanethidine, but sensitivity in the cats treated with reserpine was restored by an infusion of noradrenaline. During i.v. infusion of noradrenaline into spinal cats, the pressor responses to bretylium and guanethidine were increased, but responses to adrenaline and noradrenaline were decreased. The pressor effects both of bretylium and guanethidine were blocked by chlorpromazine. Guanethidine (3 to 5 mg/kg) injected (i.v.) into the cat relaxed the rat stomach strip. Seven experiments were run on the stomach strip in which bretylium (3 to 5 mg/kg) relaxed the strip only once;

there was no effect in four experiments and the tone of the strip was increased in two experiments. The author concludes that the initial adrenergic effects of bretylium and guanethidine are caused by a release of catecholamines from the stores of the effector organ.

Medical College
Baroda, India

- 1479 Baust, W., Niemczyk, H., & Vieth, J. The action of blood pressure on the ascending reticular activating system with special reference to adrenaline-induced EEG arousal. *Electroencephalography and Clinical Neurophysiology*, 15(1):63-72, 1963.

This communication deals with the suggestion that arousal induced by adrenaline is caused by increased blood pressure and not by a direct action of the drug. Adult cats under artificial respiration were used for isolated brain preparation. The blood pressure and EEG were recorded simultaneously. Adrenaline was injected in doses of 3 µg/kg to 10 µg/kg i.v., which led to a typical arousal. Cortical desynchronization occurred either simultaneously with the beginning of the rise in blood pressure to 1 to 3 seconds after the blood pressure had begun to rise. This latency depends on the sensitivity of the preparation to general arousal stimuli. Mechanically induced blood-pressure changes also led to an arousal. After bilateral coagulation of the mesencephalic reticular formation, these effects were abolished. When the blood pressure was kept constant artificially during an i.v. injection of adrenaline, the arousal began later and had a shorter duration than that seen when the blood pressure was not kept constant. The i.v. injection of 10 pressure units of vasopressin produced an arousal that began simultaneously with the start of the rise in the blood pressure and was less pronounced when the blood pressure was constant. This result is the same as that observed with adrenaline. The conclusion from this result is that the pressure stabilizer used cannot control any pressure changes cranial to the stabilizer, especially changes of pulse amplitude. Local injection of mammalian Ringer solution into the mesencephalic reticular formation led to an arousal, as did adrenaline when injected into the same area. The results of this study indicate that, in all probability, the blood pressure is the predominant or the only factor leading to "adrenaline-induced" arousal.

Physiological Institute of the
University of Heidelberg
Heidelberg, Germany

1480 Morrow, Dean H., Gaffney, Thomas E., & Chidsey, Charles A. **The effect of norepinephrine infusion on reserpine-induced myocardial catecholamine depletion: Implications in anesthesiology.** *Anesthesia and Analgesia*, 42(1):21-24, 1963.

Seventeen control dogs weighing 8 to 12 kg were anesthetized with pentobarbital. After the institution of positive-pressure respiration and right thoracotomy, the right atrial appendage was removed for total catecholamine analysis. Reserpine pretreatment of eight dogs weighing 9 to 12.5 kg consisted of an i.p. injection of 0.1 mg/kg of reserpine on each of the 2 days prior to the experiment. Positive-pressure respiration was supplied, and arterial pressure was continuously recorded. All animals were studied as open-chest preparations. A sample of atrial appendage was removed from each dog for total catecholamine analysis before i.v. infusion of norepinephrine, 5 µg/kg per minute, for 30 minutes. Samples of atrial appendage and arterial blood were taken from four dogs for total catecholamine analysis at 30 and 60 minutes after termination of the norepinephrine infusion. An atrial sample was taken from the other four dogs at either 70, 100, 120, or 180 minutes after discontinuation of the norepinephrine infusion. The atrial norepinephrine was reduced from the 2.1 µg/g observed in control dogs to a mean value of 0.05 µg/g in the reserpine-pretreated dogs. The norepinephrine infusion elevated the atrial norepinephrine content of the reserpinized dogs to about 30% of the control values. Persistence of this effect was approximately 180 minutes. Although useful in the treatment of hypotension occurring in patients under treatment with reserpine, norepinephrine infusion does not produce complete or sustained restoration of myocardial catecholamine stores.

National Heart Institute
Bethesda, Maryland

1481 Boura, A. L. A. & Green, A. F. **Adrenergic neurone blockade and other acute effects caused by N-benzyl-N'-N'-dimethylguanidine and its ortho-chloro derivative.** *British Journal of Pharmacology and Chemotherapy*, 20(1):36-53, 1963.

Some of the acute pharmacological actions of bethanidine---N-benzyl-N'-N'-dimethylguanidine (BW 467C60)---and its ortho-chloro derivative (BW 392C60) were investigated in laboratory animals. The actions of the two test compounds (given by various routes) in acute animal preparations and whole animals were

tested in regard to the following: peripheral sympathetic nervous system, effects on tissue pressor amines, parasympathetic nervous system, alimentary tract, neuromuscular block, toxicity, sensory nerves, and CNS. The test animals used were the cat, dog, mouse, rat, guinea pig, and monkey. Each compound exhibited the following action: inhibited release of noradrenaline during stimulation of the splenic nerve of cats; increased smooth muscle responses to adrenaline and noradrenaline; in large doses, inhibited pressor responses to standard doses of tyramine; failed to lower pressor amine content of the cat iris; in large doses i.v., blocked autonomic chlorinergic mechanisms; caused neuromuscular paralysis of voluntary muscle; and was well absorbed from the alimentary tract. The BW 467C60 did not cause diarrhea in guinea pigs. The relaxant action of BW 392C60 on the nictitating membranes of unanesthetized cats was about half that of BW 467C60 when given s.c. Except in high dosage, BW 392C60 produced little effect on cholinergic nerve function. Both BW 467C60 and BW 392C60 are chemically related to bretylium and guanethidine, but are more potent adrenergic neuron blocking agents than guanethidine.

Wellcome Research Laboratories
Langley Court, Beckenham, Kent, England

1482 Belyaev, V. I. **Changes in the electrical activity of a single node of ranvier of an isolated nerve fiber due to novocain.** *Bulletin of Experimental Biology and Medicine*, 56(8):848-851, 1963.

Investigations were carried out on isolated nerve fibers of the grass frog. The perineural sheath of the axon was removed and the nerve fiber isolated for a length of 10 to 12 mm. A 3-electrode apparatus was used for stimulation and recording. Action potentials were recorded only from the middle Node of Ranvier receiving direct stimulation. A square-wave cathodic stimulus of rheobase strength produced passive depolarization of the membrane that changed into a slowly increasing local response, developing into the ascending phase of an action potential when it reached the threshold of depolarization. Novocaine solution in concentrations of $1 \cdot 10^{-8}$ and $1 \cdot 10^{-7}$ applied directly to the Node of Ranvier did not alter the amplitude of the action potential and threshold of depolarization. A concentration of $5 \cdot 10^{-5}$ produced an increase in the threshold of depolarization, and a concentration of $1 \cdot 10^{-4}$ raised it to 200%, lowered the amplitude of the spike by 75%

to 80%, and rounded out its shape. The changes produced by novocaine in the Node of Ranvier were not fully reversible: amplitude recovery was 90% of the initial value, and the threshold of depolarization fell from 200% to 110%. As the anodic current increased to a certain limit, the action potential again rose to its initial value. Several possible explanations of the mechanism of novocaine action and the restorative effect of the direct current anode are discussed.

A. V. Vishnevskiy Institute of Surgery
Moscow, U.S.S.R.

- 1483 Benfey, B. G. & Grillo, S. A. **Antagonism of acetylcholine by adrenaline antagonists.** *British Journal of Pharmacology and Chemotherapy*, 20(3):528-533, 1963.

Isolated guinea pig atrium and ileum preparations in Tyrode solution were used in tests of acetylcholine antagonists, with pempidine added to prevent nicotinic effects of high concentrations of acetylcholine. Throughout the experiments, acetylcholine was added every 10 minutes or 3 minutes, respectively. The mean dose-response curve for acetylcholine of atrium and ileum preparations had similar positions and slopes. The dose-response curve of acetylcholine increased slowly in the presence of phenoxybenzamine without reaching a maximum, and declined very slowly when the latter was withdrawn. Atropine produced an immediate rise in the ratio, which remained constant and readily returned to normal after withdrawal. The same rapid rise and fall were produced by the combination of phenoxybenzamine and atropine. The rise in the curve produced by chlorpromazine was faster than that produced by phenoxybenzamine, and the curve declined more slowly following withdrawal. Treatment of guinea pigs with reserpine (1 mg/kg i.p.) one day before the experiment had no significant effect on atrium and ileum responses to acetylcholine or to the effects of phenoxybenzamine. Other adrenaline antagonists (phentolamine, yohimbine, and 883 F) inhibited the action of acetylcholine, but required higher concentrations than chlorpromazine. The anti-acetylcholine potency of all these drugs was not related to their antiadrenaline potency.

McGill University
Montreal, Canada

- 1484 Benmiloud, M. **The bretylium-like effect of guanethidine.** *Life Sciences*, 2(1):9-15, 1963.

The effect of guanethidine on the release of noradrenaline induced by denervation and reserpine treatment was studied by fluorimetric assay of catecholamines. In Sprague-Dawley male rats, weighing 240 to 320 g, the right superior cervical ganglion was extirpated and the contralateral gland used as a control. Reserpine and guanethidine sulfate were injected i.p. 1 hour before killing the animals. In the denervated animals, the drugs were administered s.c. at the time of operation. Control rats were injected with 0.2 ml of the reserpine solvent. Results showed that 1 hour after injection of 1 mg/kg reserpine there is marked depletion of noradrenaline in the heart (57%), spleen (70%), and submaxillary glands (76%). Simultaneous injection of guanethidine (20 mg/kg) and reserpine (1 mg/kg) diminished this depletion significantly in the spleen, and to a greater extent in the submaxillary glands. Guanethidine could, if given alone, produce a decrease of 30% in the heart, 35% in the spleen, and 41% in the submaxillary glands. High doses of guanethidine (20 mg/kg) caused a marked depletion, equally great in denervated and innervated submaxillary glands, although there was only moderate spontaneous loss of the amine. Lower doses (5 mg/kg) produced a decrease of about 50% in the intact gland, but had no influence on depletion in the denervated gland, which was complete after 24 hours.

3 rue des Cedres
Algiers, Algeria

- 1485 Gunne, Lars-M. & Reis, Donald J. **Changes in brain catecholamines associated with electrical stimulation of amygdaloid nucleus.** *Life Sciences*, 2(11):804-809, 1963.

To determine whether changes in brain catecholamines were associated with electrically induced behavior, measurements were made of brain noradrenaline (NA) and dopamine (DA), and adrenal gland NA and adrenaline (A) after repeated electrical induction of a defense reaction in cats. An electrode was implanted in the right amygdaloid nucleus of 12 cats, weighing 2.1 to 3.9 kg. Via these electrodes, six cats were stimulated by square-wave pulses at a frequency of 6 to 8 cycles per second for 3 minutes, with 4 to 5 minute intervals of rest. After 3 hours of stimulation, the cats were killed. The six unstimulated cats were killed after recovery from surgery, and three control cats

were also sacrificed. At intervals of 15 to 120 minutes after the first stimulation, the cats exhibited wild attacking movements, and some autonomic behavioral elements continued during the nonstimulus period. Implantation of electrodes, without stimulation, did not seem to influence the brain or adrenal catecholamine levels. Animals subjected to intermittent stimulation for 3 hours showed a significant reduction of adrenal A, and of NA in the brain stem and the intact, contralateral cerebral hemisphere. The drop in adrenal NA was probably significant. Brain DA was not significantly altered.

Karolinska Institutet
Stockholm, Sweden

- 1486 Holmstedt, B., Lundgren, G., & Sundwall, A. Tremorine and atropine effects on brain acetylcholine. *Life Sciences*, 2(10):731-736, 1963.

The effects of tremorine, oxotremorine (a metabolite of tremorine), and atropine on the level of brain acetylcholine were studied in male rats (200 g in weight). Tremorine (i.p.) was found to increase brain acetylcholine by an action that is not due to inhibition of brain acetylcholinesterase. The minimal dose to cause increase was 5 mg/kg. The maximal level of acetylcholine, about 40% above control value, occurred after doses of from 15 to 20 mg/kg. Oxotremorine (i.p.) was about 30 times as active as tremorine and also increased brain acetylcholine by about 40%. Atropine in doses above 50 mg/kg decreased brain acetylcholine by 20%. Doses of 2.5 mg/kg were sufficient to counteract both the increase in acetylcholine and the pharmacological effects of 20 mg/kg tremorine.

Karolinska Institute
Stockholm, Sweden

- 1487 Crossland, J. & Redfern, P. H. Chromatographic behavior of acetylcholine in brain extracts. *Life Sciences*, 2(10):711-716, 1963.

The acetylcholine-like activity of brain extracts was destroyed and then restored by addition of pure acetylcholine; the chromatographic and pharmacological behavior of this system was compared with untreated brain extracts. Brains from rats, rabbits, and guinea pigs were homogenized in trichloroacetic acid and extracted in ether. The biological activity of both untreated and treated extracts was assayed against

acetylcholine on the neostigminized frog rectus muscle, using the method of Feldberg to correct for sensitizing substances. In all 13 experiments, the rectus-stimulating material in untreated brain extracts ran, in butanol, to the same position as that reached by the authentic acetylcholine added to treated extracts. Differential bioassay of active eluates from six experiments revealed no difference between the relative activities of acetylcholine and the active material of untreated extracts. These findings lend no support to the view that a substantial part of the acetylcholine-like activity of brain extracts is due to substances other than acetylcholine itself.

University of Nottingham
Nottingham, England

- 1488 Fleming, Donovan E. Response arrest associated with the corticifugal projection of chemically induced local seizure discharge. *Electroencephalography and Clinical Neurophysiology*, 15(1):84-90, 1963.

The effect of the downstream projection of local seizure discharge from somatosensory, auditory, and visual receiving areas was studied on the performance of a learned flexion response in cats. Nine adult cats were trained to flex the right hind leg to a 6/second click conditioning stimulus (CS). Bipolar electrodes were surgically implanted in various areas of the cortex. The effect of 0.01 ml of a 5% acetylcholine (ACh) solution injected into the cerebrospinal fluid overlying the cortical target area on the CS was then tested; a 10% sucrose solution served as a control substance. Seizure discharge induced by ACh, associated with the corticifugal projection of impulses to the subcortical reticular system, produced a behavioral arrest in which the flexion CR was abolished. In the absence of the corticifugal projection of impulses, the flexion response was not affected. Conditioned respiratory responses were unaffected by the projection of seizure discharge to the subcortex. Occasionally, generalized seizures were produced as a result of local seizure discharge. However, in every case of generalized seizures, the seizure was preceded by subcortical electrophysiological changes.

University of Utah College of Medicine
Salt Lake City, Utah

- 1489 Ansell, G. B. & Marshall, Elizabeth F. Some effects of chlorpromazine on brain phospholipid metabolism—II. Labelling of choline- and ethanolamine-containing phospholipids by radioactive precursors in vitro. *Journal of Neurochemistry*, 10(12):883-888, 1963.

The effect of chlorpromazine on the uptake of p^{32} -labeled phosphorylcholine and p^{32} -labeled phosphorylethanolamine into the phospholipids (phosphatidylcholine and phosphatidylethanolamine) of rat-brain slices and dispersions was studied in vitro. Low concentrations of chlorpromazine (10^{-4} M) were found to inhibit by more than 50% the transfer of labeled phosphorylcholine and phosphorylethanolamine to the corresponding brain phospholipids. The effects were not observed when the monoesters in the form of their cytidine diphosphate esters were used in the tissue dispersions. The cytidine diphosphate esters were not effective precursors when added to the medium containing slices. Since chlorpromazine did not affect the formation of cytidine triphosphate by brain tissue in vitro, it is thought likely that the drug acts on the enzyme phosphorylcholine cytidyl transferase.

Uffculme Clinic
Birmingham, England

- 1490 Bhargava, K. P. & Chandra, Om. Antiemetic activity of phenothiazines in relation to their chemical structure. *British Journal of Pharmacology and Chemotherapy*, 21(3):436-440, 1963.

The antiemetic properties of 12 phenothiazine derivatives were compared in dogs under the same environmental and experimental conditions, and an attempt was made to correlate antiemetic action with chemical structure. Adult dogs (8 to 16 kg in weight) were given various s.c. doses of the phenothiazines 30 minutes before injection of 100 μ g/kg apomorphine. At least three doses of each compound that protected a proportion of the animals were tested. The prophylactic dose that protected 50% of the animals (PD_{50}) was calculated for each phenothiazine, and the activities were compared with a chlorpromazine HCl standard. Thioproperazine methanesulfonate was 300 times more active than chlorpromazine HCl, and perphenazine sodium citrate was 160 times more active than chlorpromazine. Thioridazine and chlorpromazine sulfoxide (a chlorpromazine metabolite) were inactive. A

discussion is given of various chemical structures that appear necessary for antiemetic action.

University of Lucknow
Lucknow, India

- 1491 Innes, I. R. Action of dexamphetamine on 5-hydroxytryptamine receptors. *British Journal of Pharmacology and Chemotherapy*, 21(3):427-435, 1963.

To test whether dexamphetamine is a sympathomimetic drug acting on adrenaline receptors, the actions of dexamphetamine, 5HT, and adrenaline were compared on the 5HT receptors and adrenaline receptors of isolated preparations of rat stomach, dog retractor penis, rabbit aorta, rabbit uterus, and guinea-pig ileum. Dexamphetamine contracted all five preparations. The 5HT also contracted all five preparations. Adrenaline inhibited rat stomach and all but the terminal 10 cm of guinea-pig ileum, but contracted dog retractor penis, rabbit aorta, rabbit uterus, and the terminal portion of the guinea-pig ileum. Responses to dexamphetamine and 5HT were not blocked in preparations protected by a high concentration of either drug during exposure to phenoxybenzamine in a dose that usually caused block. Responses to dexamphetamine and 5HT were blocked in preparations protected by adrenaline. Responses to dexamphetamine in dog retractor penis, rabbit aorta, and rabbit uterus were not reduced in preparations from animals treated with reserpine or after cocaine, indicating that the contraction is not mediated by released noradrenaline. It is concluded that dexamphetamine acts directly on 5HT receptors in these smooth muscles and, therefore, cannot be regarded as a true sympathomimetic amine.

University of Manitoba
Winnipeg, Manitoba, Canada

- 1492 Frank, G. B. & Sanders, H. D. A proposed common mechanism of action for general and local anesthetics in the central nervous system. *British Journal of Pharmacology and Chemotherapy*, 21(1):1-9, 1963.

Two series of experiments were run to test the suggestion that general and local anesthetics have a fundamentally similar action

on neurones in the CNS. In the first series, procaine HCl or cinchocaine HCl were injected i.p. into mice, either alone or after phenobarbitone, to determine whether local anesthetics would potentiate or antagonize the action of the general anesthetic phenobarbitone. In the second series, isolated slabs of cat cerebral cortex were used to compare the effects of procaine, ether, and pentobarbitone on the evoked electrical responses of cerebral cortical neurones. In both series, leptazol, a convulsive agent with no local anesthetic action, was used for comparison. Procaine or cinchocaine given alone to intact white mice produced "excitement" and convulsions, but when given 60 minutes after phenobarbitone, they caused CNS depression. Large, convulsant doses of procaine or cinchocaine abolished the righting reflex in mice previously treated with small, subanesthetic doses of phenobarbitone. In contrast, leptazol only antagonized the depression produced by phenobarbitone. When applied directly to neuronally isolated slabs of cat cerebral cortex, procaine or pentobarbitone reduced the sizes of the surface-negative and surface-positive responses to direct electrical stimulation of the cortex. Leptazol had the opposite effect. When given systematically, procaine only increased the electrical threshold for the surface-positive response recorded from the isolated slab; ether either increased or did not change this threshold, and leptazol either decreased or did not change it. These results are consistent with the suggestion that general and local anesthetics have a fundamentally similar action on neurones in the CNS.

University of Manitoba
Winnipeg, Manitoba, Canada

- 1493 Dóda, M., Feher, O., György L., & Nádor, K. **The pharmacology of new adrenergic neurone blocking agents, N-p-cyclohexylbenzyltropinium derivatives.** British Journal of Pharmacology and Chemotherapy, 21(1):10-26, 1963.

The pharmacology of three of the new adrenergic neurone blocking agents, the ones most favorable with regard to potency and toxicity, has been studied in regard to their hypotensive effect. Cats anesthetized with chloralose and urethane, or with chloralose alone, or hexobarbital alone were injected i.v. with 3a-o-benzoyl-N-p-cyclohexylbenzyltropinium bromide (N-718), 3a-o-benzoyl-N-p-cyclohexylbenzyl-N-ethylnor-tropinium bromide (N-830), or 3a-o-p-toluy-

N-p-cyclohexylbenzyltropinium bromide (N-856) at a rate of 40 µg/kg/minute to 50 µg/kg/minute. A pressor response was elicited at 0.5 to 3 mg/kg of N-718 or N-830. The N-856 increased blood pressure only in doses of 2 mg/kg or higher. Immediately after the pressor effect, a strong and long depressor response developed that was produced by 1 or 2 mg/kg of any of the compounds. Doses of 2 to 6 mg/kg i.p. caused a strong and lasting depressor response for all compounds. The N-718 and N-830 were effective at 4 to 10 mg/kg s.c., and 8 to 20 mg/kg s.c. were required for compound N-856. With intragastric or intraduodenal administration, 20 to 25 mg/kg produced lasting hypotension for all compounds. Doses administered i.p., s.c., intragastrically, or intraduodenally were found to produce no pressor response. The effects on unanesthetized cats were the same, but they were weaker than those on the anesthetized cats. The N-718 had a much more marked pressor effect on dogs anesthetized with chloralose and morphine than it did on the anesthetized cat. The N-718 and N-856 (4 to 8 mg/kg) and N-830 (2 to 3 mg/kg) produced lasting hypotension in rats. All compounds inhibited the actions of postganglionic sympathetic stimulation on the nictitating membrane and on the spleen. They did not inhibit the actions of adrenaline on these organs, but displayed a weak antityramine activity. There were slight or no parasymphomimetic, parasympholytic, ganglionic blocking or curare-like side effects.

Institute for Experimental Medicine of the
Hungarian Academy of Sciences
Department of Drug Research
Budapest, Hungary

- 1494 Haefely, W., Hürlimann, A., & Thoenen, H. **The responses to tyramine of the normal and denervated nictitating membrane of the cat: Analysis of the mechanisms of sites of action.** British Journal of Pharmacology and Chemotherapy, 21(1):27-38, 1963.

The present study compares the effects of intravenous and close-arterial injections of tyramine (0.003 to 10 mg/kg) or innervated and denervated nictitating membranes, with or without prior treatment with reserpine. Denervation of the nictitating membrane was accomplished in 60 cats of either sex weighing 1.5 to 4 kg by removing the superior cervical ganglion of the right side, together with a 1 cm-long piece of the pre-ganglionic and postganglionic sympathetic nerve. Denervation increased the sensitivity of the membrane to small doses of tyramine administered i.v. and reduced the sen-

sitivity to higher doses. Generally, denervated membranes were much less sensitive to i.a. injections over the whole dose range. In the normal membrane, identical effects were obtained with i.a. tyramine at doses about 30-times smaller than i.v. tyramine. The maximum contraction induced by i.a. tyramine was smaller than that of i.v. tyramine, and at the highest dosages, contractions were less than maximal. After treatment with 3 mg/kg of reserpine on two consecutive days, the effect of tyramine was greatly reduced. Tyramine administered i.a. required dosages about 30-times smaller for equal contractions. Prior treatment with reserpine did not influence the effect of i.a. tyramine, but in the i.v. series, reserpine depressed the responses to all but threshold doses of tyramine. In denervated membranes, the sensitivity to noradrenaline was decreased after tyramine. The opposite was true to normal membranes.

F. Hoffman-La Roche Ltd.
Basle, Switzerland

- 1495 Bhargava, K. P. & Dhawan, K. N. Depression of the vasomotor centre by mecamlamine, independent of its ganglion-blocking activity. *British Journal of Pharmacology and Chemotherapy*, 21(1):39-44, 1963.

The purpose of the present study was to obtain more direct evidence of a central vasomotor depressant action of mecamlamine, independent of its ganglion-blocking action. Cats were anesthetized with pentobarbital sodium (35 mg/kg i.p.) and bilaterally vagotomized. Ten cats received mecamlamine i.v., which produced a detectable ganglionic block at 0.3 mg/kg, but the vasomotor response to spinal compression was also blocked. When introduced into the spinal theca at total dose of 0.1 mg in a cat of 2.5 kg weight, mecamlamine inhibited the spinal vasomotor area did not produce ganglionic block. The resting blood pressure fell by 20 mm Hg. The pressor response to medullary stimulation was completely inhibited after 10 minutes when 0.03 mg/kg of the drug was injected into a vertebral artery. Recovery of the pressor response occurred after 120 minutes. The response to preganglionic stimulation was unaffected, but the resting blood pressure level was lowered by 30 mm Hg. Dogs were anesthetized with pentobarbital sodium (30 mg/kg i.v.) and bilaterally vagotomized. The reflex vasomotor responses were depressed in 8 dogs when mecamlamine was injected (3.0 mg total dose) into a lateral cerebral ventricle. Depression of the reflex responses and a

decrease in blood pressure by 20 mm Hg was observed after 30 minutes, but complete recovery occurred after 90 minutes.

King George's Medical College
Lucknow, U.P., India

- 1496 Bhargava, K. P., Chandra, Om, & Varma-Erata, D. R. The mechanism of the emetic action of sodium salicylate. *British Journal of Pharmacology and Chemotherapy*, 21(1):45-50, 1963.

The present investigation was undertaken in an attempt to elicit more information about the roles of the medullary emetic chemoreceptor trigger zone and of the peripheral receptor sites in the emesis induced by i.v., p.o., and intracerebro ventricular administration of sodium salicylate into dogs. Dogs weighing 3.0 to 12.2 kg vomited within a latent period of 18.2 ± 2.63 minutes after receiving 300 mg/kg sodium salicylate p.o., whereas with salicylate i.v. (300 mg/kg), the latency was 10.4 ± 3.96 minutes. When introduced into a lateral cerebral ventricle, 1 to 10 mg/kg sodium salicylate in 0.5 ml distilled water never caused emesis. Dosages of 300, 400, 600, and 1,200 mg/kg salicylate given i.v. never caused vomiting in 13 dogs in which ablation was successful. Ablation of the chemoreceptor trigger zone afforded protection from vomiting to only 2 of 7 dogs given 300 mg/kg sodium salicylate p.o. Superficial medullary lesions were made on 6 dogs that vomited after 300 mg/kg i.v. sodium salicylate, leaving the chemoreceptor trigger zone intact. None of the dogs vomited after 400 mg/kg (4 dogs) and 600 mg/kg (2 dogs) injected i.v., but in 2 dogs, 300 mg/kg p.o. still caused vomiting. Three of 12 dogs vomited when given the oral emetic dose 4 days after chronic vagotomy. After the i.v. emetic dose, 12 of 29 vomited. Twenty-four hours after spinal-cord transection, oral salicylate caused vomiting in 1 of 3 dogs, whereas i.v. salicylate produced emesis in 2 of 7 dogs. Neither intravenous nor oral dosages produced emetic action in dogs that had both of the operations. It is concluded that the site of emetic action of salicylates is peripheral.

King George's Medical College
Lucknow, U.P., India

1497 Yoshitani, Hideichi. **Studies on antiarrhythmic action of phenothiazine derivatives. (III) Relationship between antiarrhythmic action and the chemical structures, side effect and clinical results.** Japanese Circulation Journal, 27:487-498, 1963.

The author attempts to find a relationship between antiarrhythmic potency and the chemical structure of phenothiazine derivatives and to evaluate the clinical effectiveness of chlorpromazine alone or in combination with procaine amide and quinidine on various types of arrhythmias. Extrasystoles were evoked in adult healthy dogs (10 kg) for 60 minutes by injection with thiopental sodium and barium chloride. The drugs to be tested (total, 23) were injected i.v. immediately after a definite provocation of experimental arrhythmia. A positive result represents a complete cessation of arrhythmia in 1 minute. The most potent drug was 4695 R.P. (minimum effective dose, 0.1 mg/kg); drugs more moderate in potency were chlorpromazine, promazine, and acepromazine (minimum ED, 1 mg/kg); and the less potent drugs were 7024 R.P., trimeprazine, 4909 R.P., (chlorproethazine), and chlorpromazine sulf-oxide (minimum ED, 3 to 100 mg/kg). The substitution of the 10-position of the phenothiazine nucleus has a great influence on antiarrhythmic potency. Toxicity (sedative effect) appears to be slightly correlated to antiarrhythmic potency. Clinical results with 18 patients showed that the antiarrhythmic effect of chlorpromazine was potentiated by combination with procaine amide or quinidine.

Hokkaido University School of Medicine
Sapporo, Japan

1498 Il'yuchenok, R. Yu., & Ostrovskaya, R. U. **A study of the role of various divisions of the central nervous system in the mechanism of the convulsive action of Metrazol.** Bulletin of Experimental Biology and Medicine, 55(3):288-292, 1963.

The EEG and clinical manifestations of convulsive attack caused by pentamethylenetetrazol injected i.v. into the carotid artery or into the cerebral ventricles of 90 cats and rabbits were compared with those with intact brain and with those with the brain stem divided at different levels. Administration of the drug caused high-voltage peaked rhythmic discharges on the EEG, developing synchronously in both hemispheres, with periods of convulsive discharge alternating with periods of bioelectric activity depression accompanied by marked clonicotonic convul-

sions. In the intact brain tissue, these effects were observed after a dose of 10 to 20 mg/kg i.v. and of 3 mg injected into the carotid artery. In the brain-section study, external convulsions were noted in the head muscles only. Pentamethylenetetrazol retains its property to provoke convulsions even after complete separation of the pre-mesencephal section but, for this purpose, higher doses of 50 to 100 mg/kg are required. Preliminary administration of substances blocking the central adrenoreactive and cholinoreactive structures did not prevent the pentamethylenetetrazol effect, although after aminazine administration, somewhat higher doses were required to achieve a distinct convulsive effect.

Institute of Experimental Biology and Medicine
Novosibirsk, U.S.S.R.

1499 Innes, I. R. **Uptake of 5-hydroxytryptamine and adrenaline in the liver.** British Journal of Pharmacology and Chemotherapy, 21(1):202-207, 1963.

Cats of either sex were anesthetized with pentobarbitone sodium (45 mg/kg i.p.). The contraction in 12 experiments of the nictitating membrane caused by 5HT was greater when the dose was given into the jugular vein than when it was given into the portal vein, the ratio being about 2:1, and the difference being more apparent with doses of 10 to 50 mg/kg. It would seem that part of the 5HT injected by the portal route was taken up or destroyed by the liver. After administration of iproniazid and harmaline, the effects of portal and jugular injections were equal; isoniazid did not have this effect, whereas the effects of a portal injection of adrenaline was less than that of jugular injection. The addition of pyrogallol (100 mg/kg) enhanced the effects of both jugular and portal injections of adrenaline, but did not alter the ratio. Isoniazid did not increase the effects of portal injections of adrenaline. The results indicate that 5HT is taken up or inactivated by the liver.

University of Manitoba
Winnipeg, Manitoba, Canada

1500 Matthews, E. K. **The effects of choline and other factors on the release of acetylcholine from the stimulated perfused superior cervical ganglion of the cat.** British Journal of Pharmacology and Chemotherapy, 21(2):244-249, 1963.

Cats of either sex, weighing between 1.6 and 4.5 kg, were anesthetized first with ethyl chloride and ether, and then with intrave-

nous chloralose (80 mg/kg). The right superior cervical ganglion was isolated for perfusion in vivo with Locke solution. The amount of acetylcholine released into the perfusate decreased during successive periods of repetitive stimulation of the pre-ganglionic nerve. When choline was added, the ganglia released, over 6 stimulation periods, about twice as much acetylcholine: 423 ± 45.1 ng as against 198 ± 36.1 ng of those perfused with unmodified Locke solution. In contrast, variation of the physostigmine concentration or of the pCO_2 and pH of the perfusion fluid had no statistically significant effect upon the initial release of acetylcholine.

Medical College, St. Bartholomew's Hospital
London E.C.1, England

- 1501 Gokhale, S. D., Gulati, O. D. & Joshi, N. Y. **Effect of some blocking drugs on the pressor response to physostigmine in the rat.** British Journal of Pharmacology and Chemotherapy, 21(2):273-284, 1963.

The effects of some drugs on the pressor responses to physostigmine, adrenaline, and noradrenaline in the rat are discussed. Bretlyium and guanethidine blocked the pressor effect of physostigmine and potentiated the responses to adrenaline and noradrenaline on the blood pressure of the rat. Morphine and atropine in small doses blocked the pressor effect of physostigmine, without interfering with the actions of adrenaline and noradrenaline. Chlorpromazine in small doses (0.5 to 2.5 mg/kg) blocked the pressor effect of physostigmine and potentiated the responses to noradrenaline, whereas those to adrenaline remained unaltered. The 3,6-Di(5-diethylaminopropoxy)pyridazine di(methiodide) (Win 4981) blocked the pressor effect of physostigmine and, in its early stages, this block was partially reversed by choline chloride. The N-diethylaminoethyl-N-isopentyl-N'-diisopropylurea (P-286), in a dose that reduced the effect of dimethylphenylpiperazinium, had no effect on the pressor response to physostigmine or on the responses to adrenaline and noradrenaline. Hexamethonium, even in large doses (100 mg/kg), only partially blocked the effect of physostigmine, whereas, mecamlamine produced a complete block; the responses to adrenaline and noradrenaline were potentiated in both instances.

Medical College
Baroda, India

- 1502 Rushton, Ruth & Steinberg, Hannah. **Mutual potentiation of amphetamine and amylobarbitone measured by activity in rats.** British Journal of Pharmacology and Chemotherapy, 21(2):295-305, 1963.

Amphetamine sulfate and amylobarbitone sodium were studied separately and together (in a constant ratio of 1:20); dexamphetamine and amylobarbitone were similarly studied in a ratio of 1:6.5. Dosages ranged for all drugs from those producing no effect to those that incapacitated. All drugs were given in single s.c. injections dissolved in saline. Adult, Lister, hooded female rats, 115 to 140 days old, were used. Results showed that mixtures could stimulate exploratory activity and their maximal effects were greater than those produced by any dosage of the drugs separately. The marked stimulant effects of the amphetamine-barbiturate mixtures on rat activity could be regarded as due to true potentiation. Whether the mixture effect was accompanied by ataxia depended largely on the constituent amount of barbiturate.

University College
London, W.C.1, England

- 1503 Poulson, Evelyn and Robson, J. M. **Prevention by antagonists of the toxic action of 5-hydroxytryptamine on pregnancy.** British Journal of Pharmacology and Chemotherapy, 21(2):150-154, 1963.

Progesterone or prolactin can protect against the toxic effects of 5HT only during the early stages of pregnancy (1 to 6 days). Experiments were carried out with methysergide and cyproheptadine. A 1% solution of methysergide was prepared by dissolving 100 mg of the bimaleate salt in 1 ml of N-methane sulphonc acid and adding 5% glucose solution to make 10 ml. Cyproheptadine was administered as a solution in distilled water. Progesterone was given as a solution in oil and 5HT was administered as the creatinine sulfate dissolved in distilled water, the doses given being the salt. The experiments were performed on albino mice. Results showed that both methysergide and cyproheptadine antagonized toxic effects produced by 5HT when given in the later stages of pregnancy in mice. It is believed that these toxic effects may be due to direct action on placental circulation, which is prevented by methysergide and cyproheptadine. In early pregnancy, the toxic effect of 5HT is believed to be on the CNS, interfering with luteal activity;

this effect is presented by methysergide. Cyproheptadine alone interrupted early pregnancy, an action prevented by progesterone.

Guy's Hospital Medical School
London, S.E.1, England

- 1504 Klemparskaya, M. N. **The influence of novocaine on immunogenesis.** Bulletin of Experimental Biology and Medicine, 56(10): 1124-1127, 1963.

Experiments were carried out for 16 days on 33 rabbits (2.5 to 2.8 kg in weight) and on 570 mice (18 to 20 g in weight). It was shown that 10 ml of a 1% novocaine solution injected s.c. or 20 ml of a 0.5% solution p.o. daily depressed immunogenesis, i.e., depressed the production of agglutinins, hemolysins, and precipitins. The depression of antibody production was most marked and prolonged when the novocaine was given by s.c. injection; it then persisted after the treatment had been discontinued. When the novocaine was given by mouth, antibody production was depressed only during the period of treatment; in some animals, the antibodies were formed after the end of the treatment. In mice, immunity to typhoid bacillus was depressed after s.c. administration of novocaine. After mice had been irradiated with 300 r, immunogenesis was depressed regardless of the way in which the novocaine was given. The results obtained may be important in relation to the depression of the immune response in treatment of radiation sickness, in tissue transplantation, and in tumor development.

(No address)

- 1505 Day, M. D. & Rand, M. J. **Tachyphylaxis to some sympathomimetic amines in relation to monoamine oxidase.** British Journal of Pharmacology and Chemotherapy, 21(1):84-96, 1963.

Tachyphylaxis to the effects of indirectly acting sympathomimetic amines has been studied on the blood pressure of the cat, rabbit, and rat, on the cat spleen and nictitating membrane, and on the rabbit heart. Spinal cats were prepared by the method of Burn. Other cats were anesthetized with a mixture of chloralose and pentobarbitone (80 and 6 mg/kg, respectively) i.p. Rabbits were anesthetized with urethane 1.5 g/kg, i.p. Rats were injected with atropine (1 mg/200g). The pressor responses to tyramine and to phenethylamine declined slowly with repeated

injection; the extent of tachyphylaxis induced by these amines depended on the dosage and on the frequency of injection. The pressor responses to α -methyltyramine and to dexamphetamine (α -methylphenethylamine) declined rapidly with successive injections. The tachyphylaxis induced by one indirectly acting sympathomimetic amine is crossed to others, but not to directly acting amines, such as noradrenaline. In animals treated with nialamide i.p. (doses: cats, 15 mg/kg; rabbits, 20 mg/kg; and rats, 50 mg/kg), a drug that inhibits monoamine oxidase, the tachyphylaxis induced by tyramine and by phenethylamine was similar to that produced by their α -methyl derivatives in normal animals. Similar results were obtained when the responses to indirectly acting sympathomimetic amines were studied on the cat spleen in situ and on the rabbit heart in vitro. Indirectly acting sympathomimetic amines impaired the responses of the cat nictitating membrane to sympathetic nerve stimulation; this effect was most evident with α -methylated amines.

University of London
London, W.C.1, England

- 1506 Jarrett, R. J. **Some endocrine effects of two phenothiazine derivatives, chlorpromazine and perphenazine in the female mouse.** British Journal of Pharmacology and Chemotherapy, 20(3):397-506, 1963.

The effects of chlorpromazine and perphenazine were studied with both immature and mature Albino mice. Vaginal smears were taken 6 days of the week. Organs were removed from the animals immediately after death. At a dose of 5 mg/kg daily, each drug delayed the onset of sexual maturity in immature animals. In mature mice, a daily dose of 10 mg/kg inhibited vaginal estrus and reduced the weights of the ovaries, vagina, and uterus. Each of the two drugs inhibited ovarian hypertrophy following unilateral ovariectomy, but only slightly diminished the responses to exogenous estrogen and to exogenous gonadotrophin. In one experiment, pseudopregnancy, as shown by a positive deciduoma test, was provoked by perphenazine, but this experiment could not be repeated. Chlorpromazine failed to evoke a positive deciduoma response. At a dose of 10 mg/kg, neither drug caused a fall in levels of adrenal ascorbic acid. In the rat, treatment for 1 week with 10 mg/kg daily of either drug led to a rise in pituitary gonadotrophic activity. It was concluded that both drugs inhibited the release

of grandotrophins by the pituitary gland, independently of any action in releasing corticotrophin.

Guy's Hospital Medical School
London, S.E.1, England

- 1507 Pravdich-Neminskaya, T. V. **Effect of mediators and anesthetics on the functional state of the superior cervical sympathetic ganglion.** Bulletin of Experimental Biology and Medicine, 56(11):1256-1259, 1963.

The superior cervical sympathetic ganglion of a cat was perfused with Ringer-Locke solution without eserine. In one experiment, the effects of acetylcholine alone or of histamine alone, in the form of their hydrochlorides, were studied. Acetylcholine caused excitation of the ganglion when given in doses of the order of 0.1 mg, but its effects diminished or disappeared with an increase in the dosage. Histamine caused excitation in a dose of 0.005 mg, but 0.01 mg caused a contraction of the nictitating membrane. Novocaine, diethylaminoethanol, and xylocaine were studied for their effects on the actions of acetylcholine and histamine when applied to the ganglion together with the mediators, or 10 to 20 seconds before administration of the latter. Results show that these anesthetics possess common properties in relation to mediators, and that their use to relieve pain and other pathological states is based on their proved ability to depress the action of mediators.

A.V. Vishnevskii Institute of Surgery
Moscow, U.S.S.R.

- 1508 Il'yuchenok, R. Yu., Ostrovskaya, R. U., & Vinnitskii, I. M. **Effect of nanophyine, pachycarpine, and gangleron on the activating and convulsant effects of nicotine.** Bulletin of Experimental Biology and Medicine, 56(11):1252-1255, 1963.

The effect of nanophyine, gangleron, and pachycarpine, when injected i.v., on the background bioelectric activity, and on the activating and convulsant effects of nicotine were investigated in experiments on 70 rabbits with the brain intact, and on cats with trigeminal section of the brain stem. The degree of the EEG changes depended on the rate of administration of the preparations. With sufficiently slow administration (about 3 mg/kg/min), there was no change in the character of the background activity. In doses of 5 to 10 mg/kg, gangleron and nanophyine possessed a marked cen-

tral nicotinolytic effect, but it was manifested only in the blocking of the convulsive effect of nicotine; the activation reaction caused by nicotine was retained. These drugs also did not block the activation reaction caused by the acoustic stimulation or by electric stimulation of the sciatic nerve. The anticonvulsant effect of pachycarpine proved to be weak and inconstant. The data obtained suggest that different neurochemical mechanisms underlie the convulsive and activating effects of nicotine.

Institute of Experimental Biology and Medicine
Siberian Division
U.S.S.R. Academy of Sciences

- 1509 Krnjević, K. & Phillis, J. W. **Actions of certain amines on cerebral cortical neurones.** British Journal of Pharmacology and Chemotherapy, 20(3):471-490, 1963.

A number of derivatives of tryptamine and phenethylamine, and certain other compounds, were tested on neurones in the cerebral cortex of cats by iontophoretic release from micropipettes. Each compound was released from at least two different micropipettes, testing a total of not less than 5 neurones; the majority of compounds were tested on more than 10 neurones, mostly in the pericruciate region. The characteristic action of many of these compounds was a depression of the neuronal discharge initiated by synaptic activity or by the application of l-glutamate; imidazolylacetic acid, dopamine, ephedrine, and ergometrine were particularly effective. Catecholamines, hydroxytryptamines, and imidazolylacetic acid had a relatively quick and rapidly reversible action, not unlike that of γ -aminobutyric acid, whereas ephedrine and derivatives of lysergic acid diethylamide caused a slower and more prolonged depression of the amplitude of spikes, rather like atropine. Several compounds, including 5HT, adrenaline, and ergometrine, could also excite the same neurone when larger amounts were applied. A few substances, such as dopa and methylergometrine, had a predominantly excitant action. (46 references)

Agricultural Research Council of
Animal Physiology
Babraham, Cambridge, England

- 1510 Abrahamian, H. Arto, Allison, Truett, Goff, William R., & Rosner, Burton S. **Effects of thiopental on human cerebral evoked responses.** *Journal of Anesthesiology*, 24(5):650-657, 1963.

Subjects were 10 surgical patients scheduled for various elective procedures requiring general anesthesia. Each subject was less than 50 years old, in good general health, and free of neurologic or psychiatric illness. Stimuli were 100 μ sec constant current rectangular pulses applied to disc electrodes over the left median nerve at the wrist. Electroencephalograph needle electrodes in the scalp picked up evoked responses; an indifferent electrode was taped to the bridge of the nose. A coronal interaural circle was drawn, and a recording electrode was inserted in the scalp at a point 7 cm lateral to the midline on this circle. Each patient received 100 to 150 mg secobarbital and 0.4 to 0.6 mg atropine i.m. as premedication. Two patients received 70 and 100 mg meperidine in addition. Thiopental was then administered i.v. in successive doses of 10 to 100 mg each. Premedication produced some interference with late portions of the evoked cerebral somatosensory responses; thiopental quickly abolished these parts of the response and then slowed and reduced a still earlier deflection. These components seemed extralemniscal in origin. Initial deflections (apparently signaling lemniscal activity) remained essentially unaffected. It seemed, therefore, that some neural mechanisms of thiobarbiturate anesthesia in man are very similar to those previously found in animals.

West Haven Veterans Administration Hospital
West Haven, Connecticut

- 1511 Dagirmanjian, R., Laverty, R., Mantegazzini, P., Sharman, D. F., & Vogt, M. **Chemical and physiological changes produced by arterial infusion of dihydroxyphenylalanine into one cerebral hemisphere of the cat.** *Journal of Neurochemistry*, 10(3):177-182, 1963.

Experiments were made in order to try to trace the chemical changes produced in the brain by the arterial infusion of DOPA. Dihydroxyphenylalanine (5 to 20 mg) was infused into one carotid artery of cats through a catheter tied into one lingual artery. When dilatation of the pupil (anesthetized cats) or encephalographic arousal (cerveau isolé preparation) had developed on the side of the infusion, the brain was removed, and catecholamine estimations were carried out in different re-

gions of the two cerebral hemispheres. The dopamine content of the caudate nucleus was increased on the side of the infusion, often by more than 100%. The dopamine content of hypothalamus and midbrain-reticular formation of the treated side was increased by a similar proportion. The noradrenaline content of the hypothalamus and of the midbrain was not raised by the infusion.

Agricultural Research Institute of Animal Physiology
Babraham, Cambridge, England

- 1512 Costal, Maurice, Ausman, James, Woldring, Sabbo, & Owens, Guy. **Mono-ventricular hypothermic perfusion. Cortical electric responses to analeptic agents.** *Journal of Neurosurgery*, 20:675-678, 1963.

Pentylentetrazol, strychnine, and bemegride were administered i.v. (in amounts sufficient to produce cortico-electric spike and/or seizure responses under normothermic conditions) to 30 adult mongrel dogs. The same quantities were then given during hypothermic ventricular perfusion. Iodopyracet was administered i.a. following cannulation of the internal carotid arteries on one or both sides. Unilateral ventricular perfusion at initial temperatures of perfusate 5° C to 30° C was associated with decreased frequency and amplitudes of electroencephalographic waves on the perfused side; seizure responses to the administered drugs were absent on the cooled side; hypothermic perfusion of the 3rd and 4th ventricles (at 5° C to 15° C) immediately reduced bilateral cortical electric activity, and seizure activity induced by the analeptic agents was abolished.

Roswell Park Memorial Institute
Buffalo, New York

- 1513 Shanthaveerappa, T. R., Nandy, K., & Bourne, G. H. **Histochemical studies on the mechanism of action of the hallucinogens d-lysergic acid diethylamide tartrate (LSD-25) and d-2-bromo-lysergic acid tartrate (BOL-148) in rat brain.** *Acta Neuropathologica*, 3:29-39, 1963.

The normal localization of specific and nonspecific cholinesterases was studied in rat brains by Gerebtzoff's modification of Koelle's method (1959) and by the Coupland and Holmes method (1957), and that of monoamine oxidase was studied by the technique of Glenner et al. (1957). The effects of LSD-25 and d-2-bromo-lysergic acid tartrate

(BOL-148) have been studied on the above enzymes, and it has been observed that all of these reactions are inhibited by both drugs. The drugs were administered by i.p., i.v., as intracardiac injections. The dosage used was 0.1 mg/kg of body weight. It has been pointed out that the degree of positive reaction for acetyl cholinesterase and monoamine oxidase is more intense in the basal ganglia and thalamus, and that the inhibitory effect of the drugs was also profound in these regions. It has been suggested that these drugs inactivate the cholinesterases and monoamine oxidase, thus preventing acetylcholine and adrenalin destruction, which controls synaptic impulses. The profound inhibition of acetylcholinesterase in the thalamus and basal nuclei may set up a phenomenon allowing excessive impulses to enter the cerebral cortical centers from the subcortical level, producing the state of psychosis found by the experimental administration of the drug. It has also been suggested that the inhibition of monoamine oxidase results in more accumulation of adrenalin, which is probably oxidized to adrenochrome, the latter acting as an hallucinogen in the body.

Emory University
Atlanta, Georgia

- 1514 Weitzner, Stanley W., McCoy, George T., & Binder, Lee S. **Effects of morphine, levallorphan, and respiratory gases on increased intracranial pressure.** *Journal of Anesthesiology*, 24(3):291-298, 1963.

Mongrel dogs, weighing 10 to 20 kg, were anesthetized with i.v. pentobarbital (25 mg/kg). A series of experiments was undertaken to compare the effects of morphine and levallorphan in normal dogs and in dogs with artificially elevated intracranial pressure. A hyperosmolar solution (Cytal) was injected into the subarachnoid space to increase cerebrospinal-fluid volume; this resulted in a relatively controllable and stable elevation of cerebrospinal-fluid pressure. It was shown (1) that the dog with elevated intracranial pressure responds to hypercarbia and hypoxia the same as does the dog with normal intracranial pressure; (2) the increase in cerebrospinal-fluid pressure following morphine is due to its depressant effect on ventilation; (3) whenever hypercarbia due to morphine is prevented by artificial ventilation, or reversed by a narcotic antagonistic (levallorphan), the cerebrospinal-fluid pressure is prevented or reversed. It was concluded that morphine, therefore, is not intrinsically harmful in

the presence of increased intracranial pressure and may be used under proper circumstances in the neurosurgical patient.

State University of New York, Downstate Medical Center
Brooklyn, New York

- 1515 Feldman, Shaul & Wagman, Irving H. **The effect of pentobarbital on evoked potentials in brain of *Macaca mulatta*.** *Electroencephalography and Clinical Neurophysiology*, 15(5):747-760, 1963.

Experiments were performed on eight monkeys. Potentials evoked by peripheral stimulation were recorded in the reticular formation, hypothalamus, thalamus, basal ganglia, amygdala, and arcuate cortex. Both short latency (10 to 15 msec) and longer latency (20 to 80 msec) responses in immobilized, locally anesthetized monkeys were observed in the reticular formation, hypothalamus, and thalamus. Small doses of pentobarbital abolished or depressed these responses. Increased amounts of pentobarbital caused long latency (up to 250 msec) "secondary" responses. A high dose finally caused these responses to disappear altogether. These "secondary" responses were also recorded in arcuate cortex, amygdala, and basal ganglia. The indication is that there are at least two types of synapses in the brainstem having different susceptibilities to pentobarbital.

Mount Sinai Hospital
New York, New York

- 1516 Marley, E. & Key, B. J. **Maturation of the electrocorticogram and behaviour in the kitten and guinea-pig and the effect of some sympathomimetic amines..** *Electroencephalography and Clinical Neurophysiology*, 15(4):620-636, 1963.

Experiments were performed on 41 kittens and 20 guinea pigs carrying implanted cortical recording electrodes. Drugs tested were: l-adrenaline bitartrate, atropine sulfate, d- or d,l-amphetamine sulfate, the hydrochlorides of cocaine, d,l-cobefrine, dopamine, l-ephedrine, epinine, d,l-metanephine, d,l-methoxamine, d,l-normetanephine, l-phenylephrine, and tyramine. Other drugs used were: d,l-isoprenaline sulfate, l-noradrenaline bitartrate, hyoscyne hydrobromide, nicotine hydrogen tartrate, pentobarbitone sodium, d,l-pholedrine sulfate, physostigmine sulfate, and tuaminoheptane

sulfate (tuamine). Doses of adrenaline, noradrenaline and isoprenaline are recorded as base; the rest as salt. Good correlation occurred between electrocortical activity and behavior in the newborn guinea pig; correlation between behavior and the electrocorticogram in the kitten was not established until approximately the second week and the adult pattern of arousal did not appear until the third or fourth week. All groups of amines produced behavioral and electrocortical activation in the newborn guinea pig as in the adult, and in the adult of other species, but, in the newborn kitten, the amines were without effect until about the third to fifth week. Tyramine produced electrocortical sleep activity occasionally at the second week. Nicotine was without effect in the newborn kitten but produced behavioral drowsiness in 1 to 2 week-old animals. At 4 to 5 weeks, response was similar to that evoked in the adult. Atropine was without effect in the kitten until about the fourth week, but physostigmine produced electrocortical arousal in 15-day-old kittens. Amphetamine-like amines and catechol-like amines appeared to produce central effects through different receptors or mechanisms.

Institute of Psychiatry, Denmark Hill
London, S.E. 5, England

- 1517 Rogoman, E. P., Johnston, A. E., & Conn, A. W. **The use of epinephrine during halothane anaesthesia with respect to ventricular irritability in dogs. A preliminary report.** *Anesthesia and Analgesia*, 42(1):109-116, 1963.

Subcutaneous and intramuscular injections of epinephrine were given to eight dogs under various conditions. Evidence of ventricular irritability was observed in control animals and in those receiving epinephrine. One dog receiving epinephrine and 2% halothane developed ventricular tachycardia and multifocal ventricular extrasystoles. Intravenous injections of epinephrine were given to 12 dogs under various conditions. Halothane sensitized the dog heart to epinephrine to a much greater extent than thiopentone. Ventricular irritability occurs with halothane and thiopentone. During halothane anesthesia, the injection of epinephrine produced ventricular arrhythmias of a more serious nature than during thiopentone anesthesia, and the effects of the combination are unpredictable.

The Hospital for Sick Children
Toronto, Ontario, Canada

- 1518 van Orden, Lucas S. & Sutin, Jerome.

Differential effects of norepinephrine on responses evoked in the hypothalamic ventromedial nucleus. *Electroencephalography and Clinical Neurophysiology*, 15(5): 796-803, 1963.

The injection of 20µg to 55µg norepinephrine directly into the hypothalamic ventromedial nucleus (HVM) or the ipsilateral carotid artery increased the amplitude of the HVM response to septal stimulation and suppressed the HVM response to amygdaloid stimulation. Similar results were obtained with comparable concentrations of epinephrine. The d-amphetamine produced a suppression of both septal-HVM and amygdaloid-HVM responses. Local injection of 0.85% saline, pitressin, or sodium nitrite did not alter the HVM evoked responses.

Yale University School of Medicine
New Haven, Connecticut

- 1519 Iasser, Elliott, C., Elizondo-Martel, Gonzalo, & Granke, Richard C. **Potentiation of pentobarbital anesthesia by competitive protein binding.** *Journal of Anesthesiology*, 24(5):665-671, 1963.

A statistically significant prolongation of anesthesia was noted in rats injected with sodium acetate as well as pentobarbital in comparison to rats injected with pentobarbital alone or pentobarbital with saline. Sodium diatrizoate injected in molar dosages equivalent to sodium acetate failed to potentiate pentobarbital narcosis. Iodipamide when injected in dosages equivalent to sodium acetate in rats under pentobarbital anesthesia proved quite toxic. No potentiation of ether anesthesia was produced by injection of sodium acetate. The hypothesis can therefore be formulated that potentiation is achieved by the unfavorable competitive position of pentobarbital with sodium acetate for the protein binding sites in hepatic and renal excretory cells and in circulating plasma. This results in both sustained elevations of total plasma-pentobarbital levels secondary to diminished conjugative and excretory mechanisms and in increased amounts of unbound pentobarbital available to the tissues, including the central nervous system.

University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

- 1520 Andersen, Nikaan & Johansen, Sophus H. **Incidence of catechol-amine-induced arrhythmias during halothane anesthesia.** *Journal of Anesthesiology*, 24(1):51-56, 1963.

The effects of epinephrine and norepinephrine on cardiac irritability during halothane anesthesia were compared. It was found that for practical clinical purposes, increased myocardial excitability occurs as readily with one amine as with the other. The hypotension of halothane anesthesia can only be partly corrected by an infusion of epinephrine or norepinephrine if ventricular arrhythmias are to be avoided. The risk of evoking ventricular arrhythmias is increased with infusion rates of more than 10 µg/minute in the presence of arteriosclerotic cardiac disease.

University of Florida
Gainesville, Florida

- 1521 Bittrich, N. M., Kane A. V'R., & Mosher, R. E. **Methohexital and its effect on liver function tests. A comparative study.** *Journal of Anesthesiology*, 24(1):81-90, 1963.

A comparative study was made in 114 patients of the effect on liver-function tests of three ultrashort-acting intravenous barbiturates (methohexital, thiopental, and thiamylal). In general, all three drugs changed liver function in the same manner. On a weight-of-drug basis, methohexital produces more depression of liver function than thiopental or thiamylal. Based on amounts of drug required for anesthesia, methohexital produces less depression of liver function. In patients with pre-existing liver-function depression, methohexital did not increase this depression more than in patients with normal liver function.

Providence Hospital
Detroit, Michigan

- 1522 Foldes, Francis F., Foldes, Vera M., Smith, J. Crispin, & Zsigmond, Elmer K. **The relation between plasma cholinesterase and prolonged apnea caused by succinylcholine.** *Journal of Anesthesiology*, 24(2):208-216, 1963.

The plasma cholinesterase activity of 20 patients who developed prolonged apnea after the i.v. administration of relatively small doses of succinylcholine was investigated.

The substrates used were acetylcholine, butyrylcholine, succinylcholine, benzoylcholine, and procaine. The inhibitors employed were: neostigmine, R02-0683, dibucaine, and succinylcholine. Of the 20 patients, plasma cholinesterase activity was qualitatively and quantitatively within normal limits in four. This indicates that succinylcholine-induced prolonged apnea is frequently but not always associated with the presence of atypical plasma cholinesterase. Of the 16 patients with atypical plasma cholinesterase, 12 were atypical homozygotes and four were heterozygotes. The plasma samples of 24 relatives of 6 patients were also studied. Of these, 12 were heterozygotes, 9 were normal, and 3 were atypical homozygotes. The enzymatic hydrolysis rate of all substrates was markedly reduced in the atypical homozygotes and less markedly, reduced in the heterozygotes. The hydrolysis rate of procaine was more reduced than those of the other substrates. The effect of all inhibitors studied was less on the atypical than on the normal enzyme. Procaine substrate and R02-0683 or decamethonium inhibitors may be more suitable for the detection of atypical plasma cholinesterase than benzoylcholine substrate and dibucaine inhibitor. The administration of large amounts of hydrolyzable local anesthetic agents to subjects with atypical plasma cholinesterase may also cause severe systemic toxic reactions. To prevent untoward reactions, the plasma cholinesterase activity of the relatives of subjects known to have this hereditary abnormality should also be investigated.

Montefiore Hospital
New York, New York

See also: 1112, 1129, 1200, 1213

PHARMACOLOGY

- 1523** Quinton, R. M. **The increase in the toxicity of yohimbine induced by imipramine and other drugs in mice.** British Journal of Pharmacology and Chemotherapy, 21(1):51-66, 1963.

In mice, yohimbine appears to accentuate the normal "alarm" reactions (alerting, flight) to external stimuli. Imipramine increases this effect and at the same time converts a nonlethal dose of yohimbine into a lethal one. The effect of imipramine is greatly reduced by adrenalectomy or by treatment with reserpine, syrosingopine, ganglion-blocking drugs or adrenaline antagonists acting on sympathetic β -receptors. Hypnotic, anticonvulsant or anaesthetic agents, tetrabenazine or antagonists of 5-hydroxytryptamine do not reduce the imipramine effect. A variety of drugs which, like imipramine, are known to interfere with the tissue binding of noradrenaline also increase the toxicity of yohimbine. Yohimbine significantly reduces brain noradrenaline content; adrenal catechol amines are slightly reduced. The results suggest that yohimbine releases noradrenaline from stores or nerves as a consequence of increased central sympathetic activity. Imipramine increases the actions and toxicity of yohimbine by increasing the effects of the released noradrenaline on β -receptors. The lethal effects of a high dose of yohimbine alone are not reduced by any of the treatments tested, and appear not to result from activation of sympathetic mechanisms. (49 references)

Pfizer
Sandwich, Kent, England

- 1524** Broadbent, J. L. **The interaction of some stimulant and depressant drugs on the frog heart.** British Journal of Pharmacology and Chemotherapy, 21(1):78-83, 1963.

The activity of frog isolated hearts was depressed by altering the perfusing Ringer solution in five different ways: by reducing the calcium content, by increasing the potassium content, and by adding ether, thiopentone, or acetylcholine. Depressed hearts were perfused with Ringer solution

containing the following stimulant drugs: paullinia tannin, tannic acid, hydrogen peroxide, sodium oleate, sodium caprylate, and ouabain. All these stimulant drugs had similar actions on hearts depressed by calcium shortage, ether, and thiopentone; hearts depressed by acetylcholine were, however, only weakly stimulated. Hearts depressed by potassium were readily stimulated by oleate, caprylate, and paullinia tannin; ouabain and hydrogen peroxide had weak stimulant actions on hearts depressed by potassium, and tannic acid had a negative inotropic action. The differing actions on hearts depressed by potassium are probably related to differences in the degrees of fixation of the stimulant drugs. The mode of action of ouabain and the functional lesion in hearts depressed by narcotics are discussed.

Smith Kline & French Research Institute
Welwyn Garden City, England

- 1525** Wallgren, Henrik. **Rapid changes in creatine and adenosine phosphates of cerebral cortex slices on electrical stimulation with special reference to the effect of ethanol.** Journal of Neurochemistry, 10(5):349-362, 1963.

Levels of ATP, ADP, AMP, and CrP were measured in slices of rat cerebral cortex, and effects of electrical stimulation, of cyanide and PCMB, and of 0.4% ethanol were observed. The levels of adenosine phosphates were not affected by stimulation or by ethanol. The CrP decreased at a rate of 1250 μ moles/g tissue/hr between 2 and 4 seconds of stimulation and was stabilized at the lower level. Resynthesis of CrP after stimulation for 7 seconds proceeded at a rate of about 270 μ moles/g tissue/hr. Ethanol reduced the rate of decrease by 50% without any effect on resynthesis. Cyanide plus PCMB acting for periods up to 90 seconds caused a rapid decrease in CrP, loss of total adenosine phosphate and ATP, a transient increase in ADP, and a rise in AMP between 60 and 90 seconds of exposure. When electrical stimulation and the inhibitors, or cyanide alone, were applied simultaneously for 20 seconds, stimulation caused an in-

crease in the loss of CrP and ATP. Experiments with o-phosphate labeled with P^{32} showed that the decrease in specific activity of the terminal P of ATP caused by electrical stimulation was largely blocked by ethanol. Support is given to the viewpoint that the main effect of ethanol on the nervous system is on processes involved in electrical activity, and not on reactions supplying energy for such activity.

Research Laboratories of the
State Alcohol Monopoly
Helsinki, Finland

- 1526 Hillman, H. H., Campbell, W. J. & McIlwain, H. **Membrane potentials in isolated and electrically stimulated mammalian cerebral cortex. Effects of chlorpromazine, cocaine, phenobarbitone and promazine on the tissue's electrical and chemical responses to stimulation.** *Journal of Neurochemistry*, 10(5):325-339, 1963.

Displacement and recovery of membrane potential as a result of electrical stimulation are measured. Resting membrane potentials measured by micropipette electrodes in guinea-pig cerebral cortex in vitro, were of a mean value between -36 and -40 mV. Application of electrical pulses for 1 minute diminished the potentials observed 1 minute after stimulation ceased. The time-course of recovery of potential was measured after 10-minute stimulation—the potentials reach reached nearly zero and recovered at about -12.5 mV/minute. The potentials before application of pulses were increased by 50 μ M chlorpromazine and diminished by 0.3 mg/ml clupeine. Their change with pulses was diminished, or recovery accelerated, by 0.3 mM phenobarbitone, by 50 μ M chlorpromazine, and by 20 μ M cocaine. These agents did not significantly affect the potassium or non-inulin sodium of tissues incubated in vitro. When pulses were applied to such tissues, chlorpromazine inhibited the change in sodium and potassium; phenobarbitone permitted the changes, but afforded more complete recovery of noninulin sodium. Spike discharges were observed on 25 occasions on penetrating the isolated tissue with microelectrodes. They commenced from potentials of -32 to -55 mV, were of +27 to +70 mV, were associated with positive and negative after-potentials, and carried a notch on their rising phase. The nature and incidence of the discharge did not appear to be markedly affected by the substances named above, nor by a number of other experimental changes.

Mandsley Hospital
London, S.E.5, England

- 1527 Brownlee, G. & Harry, J. **Some pharmacological properties of the circular and longitudinal muscle strips from the guinea-pig isolated ileum.** *British Journal of Pharmacology and Chemotherapy*, 21(3):544-554, 1963.

The longitudinal preparation was sensitive to acetylcholine, methacholine, carbachol, 5HT, histamine, and nicotine; the circular preparation was insensitive to 5HT, histamine and nicotine, and responded to the choline esters only in high concentrations. Incubation of the preparation with the anticholinesterase, mipafox (NN-diisopropylphosphorodiamidic fluoride), sensitized both preparations to the action of acetylcholine; potentiation of the contraction of the longitudinal muscle was 16-times; that of the circular one 4,000-times. The longitudinal muscle was more sensitive than the circular muscle to acetylcholine, whether both were treated with mipafox or not. Both bradykinin and substance P stimulated the longitudinal but not the circular muscle, an effect not modified after mipafox. Hyoscine antagonized the responses of the circular muscle strip, treated with mipafox, to acetylcholine and to histamine, but on the longitudinal muscle strip the response to histamine was not affected, the response to acetylcholine being competitively antagonized. Morphine, in the same concentrations on both circular and longitudinal muscle strips, antagonized the stimulant actions of nicotine and, to a lesser extent, of 5HT, but the responses to histamine on the longitudinal muscle strip were not antagonized by morphine, which was in contrast to its action on the circular muscle strip. The main differences in the responses of the circular and longitudinal muscle of the guinea-pig ileum to drugs were in the intrinsic properties of smooth muscle cells.

King's College, University of London
Strand, W.C.2, England

- 1528 Abood, L. D., Smith, C. M., Koyama, I., & Koketsu, K. **Action of some psychotomimetic agents on the excitatory and biochemical processes of frog sartorius muscle.** *Journal of Neurochemistry*, 20(2):95-111, 1963.

A major question dealt with in this study concerns the extent to which biochemical effects produced by the glycolate esters on frog sartorius muscle are related to the changes in the conductive and contractile properties. The actions of some synthetic anticholinergic, psychotomimetic agents have

been investigated on the biochemical and excitatory process of frog sartorius muscle. In a calcium-deficient medium or in the presence of high external potassium, these agents, at concentrations of 10^{-6} M, will prevent the stimulation in glycolysis normally occurring in such media. This action can only be demonstrated in a functionally intact sartorius muscle. The agents diminish the rate of depolarization of individual muscle fibers in the presence of EDTA and other calcium-binding agents. At the same time, they increase the isometric contraction and prolong the negative after-potential of electrically excited muscle fibers. The mechanism of action of the frog is discussed from the standpoint of the drug's action on the excitatory membrane, and particularly in terms of its relationship to the role of calcium and phosphates in excitation.

University of Illinois College of Medicine
Chicago, Illinois

1529 Pan'shina T. N. Changes in the conditioned reflex and blood cholinesterase activity of animals under the influence of the phosphorganic insecticide, phosphamide. Bulletin of Experimental Biology and Medicine, 56(12):1347-1350, 1963.

In studying the action of phosphamide, a phosphorganic insecticide, on the higher nervous activity of animals with the aid of the conditioned-reflex method, it was established that in doses and concentrations not provoking any visible signs of poisoning, this preparation caused changes in the conditioned reflex activity of cats and depression of cholinesterase activity of the serum and erythrocytes of these animals. The phosphamide was introduced into the stomach of cats in the form of an aqueous emulsion with OP-7 emulsifier. Changes in the conditioned reflex activity were observed in depression of cholinesterase of erythrocytes and serum by 40 and more percent, i.e., depression of cholinesterase activity was an earlier and a more sensitive index of intoxication. Disturbances of the higher nervous activity observed in the animals during the action of phosphamide were manifested in intensified active inhibition (differential and extinction), reduction of conditioned reflexes according to the anesthetic phase type; by the nature of the changes, these disturbances were similar to those of the higher nervous activity in acetylcholine poisoning.

Kiev Scientific-Research Institute of Work Hygiene and Occupational Diseases
Kiev, U.S.S.R.

1530 Baskakova, G. M. & Kopytova, F. V.

Effect of chlorpromazine on respiration in the frog. Bulletin of Experimental Biology and Medicine, 56(12):1311-1314, 1963.

The effect of chlorpromazine on respiration was studied in frogs after transection of the brain stem at different levels. Sixty experiments were conducted on autumn and winter specimens of the frog *Rana temporaria*. The movements of the mandibular membrane were recorded by a myographic method, and the frequency of respiration and the heart rate were determined. Visual observations were made on the changes in skin color, on the secretion of mucus, and on the animal's general motor reaction. Chlorpromazine was used in ampule form, diluted with isotonic NaCl to give a 0.025 to 0.1% solution. The drug was injected i.v., under local anesthesia, in doses of between 0.01 and 0.2 mg per from (i.e., 0.25 to 5 mg/kg body weight). The brain was divided 1/3, 1/2, and 2/3 of the way along the optic lobes, and at the anterior border of the medulla. Medium and large chlorpromazine doses depress the respiration of intact animals. In frogs with divided brain, chlorpromazine induces periodic respiration except above the medulla.

Moscow State University
Moscow, U.S.S.R.

1531 Aghajanian, G. K. "Microsome" fraction of brain: Structural changes induced by ascorbic acid. Science, 141 (3581):628-630, 1963.

Microsomes were prepared from rat brain. A single brain was homogenized in 10 volumes of 0.25 M sucrose at 0°C with a Teflon pestle (cylinder diameter 2.54 cm; clearance 0.012 to 0.018 cm) at 1,5000 rev/min for 30 seconds (6 strokes). The supernatant of an initial 12-minute spin at 18,000 g was decanted and centrifuged at 30,000 g for 25 minutes. The resulting white pellet was "washed" in 0.25 sucrose and resedimented. The basic medium used in all experiments consisted of 0.05 M tris-Cl buffer (pH 7.4), to which microsomes and specified reagents were added. The usual vesicular configuration of membrane fragments in the brain "microsome" fraction was radically altered by treatment with ascorbic acid and adenosine monophosphate. Light-scattering measurements and electron micrographs showed that the treated membranes assume predominantly planar forms. This change in struc-

ture appeared to be contingent upon a continued transport of electrons from ascorbic acid.

Yale University School of Medicine
New Haven, Connecticut

- 1532 Redick, Thomas F., Renfrew, Alice G., Pieri, Lorenzo, & Marazzi, Amedeo S. **Cerebrally active small moiety from "taraxein-like" blood fractions.** Science, 141 (3581):646-647, 1963.

An experiment was performed with a model made of a mixture of albumin and serotonin. Separation was obtained by dialysis, using a 5-chambered electrodialysis cell or Wood cell, in which cathode and anode compartments were separated by selective, ion-exchange membranes arranged to pass anions and cations from the center into their respective compartments, but not into the electrode chambers. The serotonin accumulated in the cathode compartment where cerebral bioassay showed an activity, whereas activity in the center or feed compartment decreased during the 30-minute period of electrodialysis at 90 volts. Proceeding to the "taraxein-like" material itself, experiment was begun with the albumin, the more active of the two fractions and the more readily solubilized. In cats in which sensitivity was such that 10 μ g to 20 μ g of serotonin produced approximately 50% inhibition of cerebral synaptic transmission, bioassay indicated successful electrodialysis in 10 out of 10 trials, with activity appearing each time in the cathode compartment. Results supported the hypothesis that there is higher activity at the cathode than at the anode where dilution resulted from the presence of the inert portion of the negative moieties.

Veterans Administration Research Laboratories in Neuropsychiatry and Mellon Institute
Pittsburgh, Pennsylvania

- 1533 Korneva, E. A. & Yakovleva, M. I. **Some data on the role of higher divisions of the brain in the reaction of respiration to the administration of aminazine.** Bulletin of Experimental Biology and Medicine, 56(8):900-903, 1963.

This investigation was carried out to verify the hypothesis that the functional stability of the respiratory system may be related to the activity of the adjusted mechanisms of

the CNS. In 76 acute and chronic experiments staged on cats and rabbits narcotized i.v. with a 10% solution of urethane or with ether, a study was made of the role played by various portions of the brain in the reaction of respiration to aminazine. In administration of this preparation in a dose of 2 to 3 mg/kg to cats and in a dose of 8 to 10 mg/kg to rabbits, no significant shifts occurred in the frequency and nature of respiratory movements. The use of hypnotics, acting as a depressive agent on the brain cortex, did not change the reaction of respiration to aminazine. In decerebrated animals, aminazine injection led to marked respiratory disturbances. Such animals often perish, the cause of death being respiratory arrest. Evidently, weakly pronounced respiratory reactions following aminazine administration in intact animals were the result of considerable compensatory capacities of the higher portions of the brain in respiratory regulation.

Institute of Experimental Medicine
Leningrad, U.S.S.R.

- 1534 Dyablova, P. E. **The effect of gamma-aminobutyric acid on the potassium and acetylcholine contractions of skeletal muscle.** Bulletin of Experimental Biology and Medicine, 56(8):898-899, 1963.

An investigation was made of the effect of γ -aminobutyric acid on acetylcholine and potassium contractions of skeletal muscle. The experiments were carried out on the isolated rectus muscle of the frog's abdomen. The muscle was maintained undisturbed for a period of 1 to 2 hours in a small beaker filled with Ringer's solution, through which oxygen was bubbled. After establishing the effective concentration of acetylcholine or potassium chloride and replacement of the Ringer's solution, a freshly prepared solution of γ -aminobutyric acid was added to the beaker (acid concentration in the vessel was 1×10^{-6} to 1×10^{-3}). After 30 minutes, previous concentration of acetylcholine or potassium chloride was again added. Muscle contractions were recorded over a period of 30 seconds to 1 minute on a stationary kymograph. Results showed that γ -aminobutyric acid has a marked inhibitory effect on potassium contractions but not on acetylcholine contractions.

Leningrad Pediatric Medical Institute
Leningrad, U.S.S.R.

- 1535 Price, H. L., Cook, W. A., Jr., Deutsch, S., Linde, H. W., Mishalove, R. D., & Morse, H. T. **Hemodynamic and central nervous actions of cyclopropane in the dog.** *Journal of Anesthesiology*, 24(1):1-10, 1963.

The response of dogs to cyclopropane closely resembles the response observed in man. Studies were made of autonomic and circulatory actions of cyclopropane in 49 mongrel dogs. Cyclopropane in oxygen was administered in moderate (30% to 40%) concentrations. Perfusion of the head alone with blood containing cyclopropane increased both systemic arterial mean and pulse pressures and catechol amine concentrations, but exposure of the body alone to the anesthetic had effects diametrically opposite in direction. Both arterial hypertension and increased plasma catechol amine concentrations were prevented by brain sections involving any part of the medulla oblongata. Various autonomic nervous stimuli, which ordinarily cause arterial hypotension in dogs, were shown to be ineffective during administration of cyclopropane. It was concluded that cyclopropane elicited arterial hypertension and increased plasma concentrations of catechol amines in dogs by selectively depressing "depressor" neurones in the medulla oblongata. The "pressor" neurones apparently were affected to a lesser degree. Concerning the relevance of these findings to results previously obtained in both dog and man, it was concluded that sympathetic nervous responses to cyclopropane in the two species appear basically similar whereas parasympathetic actions are at least quantitatively different.

University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

- 1536 Rein, Julius, Austen, W. Gerald, and Morrow, Dean H. **Effects of guanethidine and reserpine on the cardiac responses to halothane.** *Journal of Anesthesiology*, 24(5):672-675, 1963.

The effects of halothane on myocardial contractile force, heart rate, and systemic arterial pressure were studied in 19 adult dogs (12.2 kg in weight) after the administration of 2 mg atropine i.v. Observations were made in control dogs, in dogs pretreated with guanethidine (100 mg/kg), or in dogs pretreated with reserpine (0.1 mg/kg). The anesthetic agent, in concentra-

tions ranging from $\frac{1}{2}\%$ to 2%, produced decreases in heart contractile force, which did not differ significantly among the three groups of animals. In concentrations of $\frac{1}{2}\%$ to 1%, halothane had a significantly greater negative chronotropic effect, and reduced arterial pressure more in the guanethidine- and reserpine-pretreated dogs than in the control dogs; comparable decrements were produced in these responses at the $1\frac{1}{2}\%$ and 2% halothane concentrations. These observations indicate that the negative inotropic effects of halothane are not modified by guanethidine, reserpine, or the depletion of myocardial catecholamines that they produce, whereas the negative chronotropic and hypotensive effects of halothane at lower concentrations are augmented by pretreatment with these drugs.

National Institutes of Health
Bethesda 14, Maryland

- 1537 King, C. T. G. **Teratogenic effects of meclizine hydrochloride on the rat.** *Science*, 141(3578):353-355, 1963.

The effects of meclizine hydrochloride on the fetal development in the rat were investigated in an effort to obtain an agent that might specifically induce oral malformations. The subjects were 68 Sprague--Dawley pregnant rats weighing 200 ± 20 g. Forty-nine pregnant rats served as controls. A preparation of meclizine hydrochloride (Bonine) was force fed by intubation as a suspension in 50% by volume of ethanol in water at different states of gestation. At no time did the volume that was force fed exceed 1 ml. The teratogenic effects of the meclizine hydrochloride were considerable. The external defects were specific, and could be induced at will in 100% of the litters and in 100% of the fetuses making up each litter. The critical period for administration was from the 12th to 15th day. Anomalies were produced in the tongue, palatal closure, mouth, lower jaw, vertebrae, and limbs.

National Institutes of Health
Bethesda 14, Maryland

- 1538 Fuortes, M. G. F. & Nelson, P. G. **Strychnine: Its action on spinal motoneurons of cats.** *Science*, 140(3568):806-808, 1963.

A study has been made of the effects of strychnine on motoneuronal membrane of cats to deduce some of the characteristics of the synaptic impingement on motoneurons after

the administration of strychnine. Before and after i.v. injection of strychnine in doses up to 0.3 mg/kg, a motoneuron was penetrated, and its responses to antidromic, orthodromic, and direct stimuli were recorded. None of the motoneurons was appreciably affected. The changes in reflex probably result from increase of excitatory impingement upon motoneurons. Spikes recorded during a rapid succession of nerve impulses produced by strychnine ("strychnine burst") suggest that soma membrane resistance is appreciable during stimulation.

National Institute of Neurological Diseases and Blindness
Bethesda 14, Maryland

- 1539 Steiner, W. G., Pscheidt, G. R., & Himwich, H. E. Influence of methodology on electroencephalographic sleep and arousal: Studies with reserpine and etryptamine in rabbits. *Science*, 141(3575):53-55, 1963.

In studies with reserpine (1.0 mg/kg) i.v. and with etryptamine, (5.0 mg/kg) i.v. electroencephalographic effects were obtained when either of these two drugs was administered to New Zealand, male, albino rabbits prior to surgical preparation for EEG recording, as opposed to the drug being given after the rabbits had been fully prepared for EEG recording. With the one method, EEG rhythms indicative of sleep were obtained; with the other method, EEG rhythms indicative of CNS stimulation were obtained. With both methods, the amount of drug, duration of drug in animal, and type of acute preparation were identical for both sets of findings. The presurgical injection procedure produced EEG results more in accordance with behavioral and biochemical findings, even though the conventional procedure is to administer the experimental drug after the animal has been prepared for EEG recording.

Galesburg State Research Hospital
Galesburg, Illinois

- 1540 Tyler, H. Richard. Botulinus toxin: Effect on the central nervous system of man. *Science*, 139(3557:847-848, 1963.

Evidence is presented to support the belief that there is a simultaneous central and peripheral neuromuscular effect of botulinus toxin. A 61-year-old man was admitted to the hospital 48 hours after eating home-canned mushrooms. The "H" reflex was pres-

ent and prominent in multiple recordings from different areas after stimulation of the peripheral nerve. Similar recordings were made of a normal subject; no "H" response was seen. It is possible that botulinus toxin may have an effect on inhibitory actions of some interneurons similar to that reported for tetanus. Certain phenomena, such as tonic spasm of the hand and cardiac irregularities, are difficult to understand if the toxin is limited only to the periphery.

Harvard Medical School
Boston, Massachusetts

- 1541 Blom, Sigfrid. Diphenylhydantoin and lidocaine in decerebrate cats. *Archives of Neurology*, 8:506-509, 1963.

A study was made of the effects of lidocaine and diphenylhydantoin on a brain-stem reflex in normal cats. Adult cats were decerebrated by intercollicular section under ether. Diphenylhydantoin and lidocaine were administered i.v. through a cannula in the femoral vein. Care was taken to administer diphenylhydantoin slowly to avoid previously described effects on blood pressure. The dose of diphenylhydantoin was between 5 and 15 mg/kg body weight and that of lidocaine was 3 to 5 mg/kg. The linguomandibular reflex was elicited (well above threshold) once per 3 to 4 seconds. Recordings from the cathode-ray oscilloscope were made on continuously running bromide paper. Both diphenylhydantoin and lidocaine were found to depress the linguomandibular reflex in decerebrate cats, the effect being more pronounced and longer lasting with diphenylhydantoin.

University Hospital
Uppsala, Sweden

- 1542 Setnikar, Ivo & Paterlini, Maria Rosa. Factors affecting toxicity of dimeflin intravenously infused. *Toxicology and Applied Pharmacology*, 6:263-268, 1963.

Dimeflin (3-methyl-7-methoxy-8-dimethylaminomethylflavone hydrochloride) dissolved in 0.9% NaCl was infused through a catheter connected by a 22-gauge injection needle to the tail vein of Swiss SMZ mice. The infusion syringe was operated by a Palmer slow-injection apparatus. The animals were left unrestricted in glass beakers. The mice used were males with a body weight between 19 and 26 g. Experiments were also

performed on adult Wistar rats of both sexes. All experiments were carried out at a room temperature between 19° and 23° C. It was found that the first twitch, tonic phase, and cardiac-arresting doses depend largely on the rate of infusion of the dimeflin. Sex and body weight seemed to have little effect on toxic doses of dimeflin.

Recordati S.p.A.
Milan, Italy

- 1543 Michaux, R. & Verly, W. G. **Action cataleptogene des ethers methyliques des mono- et polyphenolamines.** (Cataleptogenic action of methyl ethers of mono- and polyphenolamines.) *Life Sciences*, 2(3):175-183, 1963.

A study was conducted to determine whether partial or total methylation of the phenolic OH of adrenaline, noradrenaline, or one of their precursors could form products in vivo comparable to mescaline in their action on the CNS. These methyl ethers could appear in excessive amounts in the organism under certain pathological conditions. The experimental subjects were male white mice of the R3A strain, with average weight of 20 g. The compounds tested were dissolved in distilled water immediately before use, and were injected i.p. The cataleptogenic dose (CD₅₀) was calculated for groups of 10 animals by the "up and down" method. The results showed a clear relationship between CD₅₀ and chemical structure, indicating a hierarchy of members of the phenylethylamine, ethanolamine, and methylethanolamine groups in cases of similar side chain, and diminishing activity with increasing complexity of the side chain. Tyramine methyl ether (4-methoxy-phenylethylamine) is the most active, being markedly more active than mescaline, and any substitution in its molecule results in cumulative diminution in its activity. Although metanephrine and normetanephrine are formed in vivo, they were found to be the least active of the methyl ethers studied.

University of Liege
Liege, Belgium

- 1544 Biscoe, T. J. & Krnjević, K. **Chloralose and the activity of Renshaw cells.** *Experimental Neurology*, 8(5):395-405, 1963.

Renshaw cells in the lumbosacral region of the spinal cord in eight anesthetized or decerebrate cats were examined with multi-

barrelled micropipettes, testing their responses to ventral root volleys and iontophoretic applications of glutamate and ACh. The i.v. administration of one or more doses of chloralose (20 to 80 mg/kg) did not alter specifically the sensitivity to ACh, nor were there any consistent changes in the responses to ventral root stimulation, so long as the blood supply remained adequate. The sensitivity of seven cells was observed at various times before and after injecting chloralose. After moderate doses of chloralose (20 to 40 mg/kg), there were no clear changes in the sensitivity to glutamate. From these results, it is concluded that chloralose does not cause a general block of the release of ACh from central cholinergic nerve endings. It is suggested that chloralose depresses the recurrent inhibition of motoneurons by inactivating spinal inhibitory synapses.

Agricultural Research Council
Institute of Animal Physiology
Babraham, Cambridge, England

- 1545 Velluti, R. & Hernández-Peon, R. **Atropine blockade within a cholinergic hypogenic circuit.** *Experimental Neurology*, 8(1):20-29, 1963.

In 13 cats of both sexes, cannula were permanently implanted in the preoptic region, interpeduncular nucleus and medial midbrain tegmentum, and electrodes were implanted in the olfactory bulb, cortex, periorbital region, and neck muscles. The chemical substances employed were acetylcholine, atropine, and eserine in crystals. Sleep was obtained by local application of acetylcholine in all the sites listed above. Somnolence and light sleep were also obtained by application of eserine in the preoptic region. Atropine in the same loci elicited alertness and blocked sleep otherwise produced by cholinergic stimulation of the same atropinized point of rostral segments of the hypogenic circuit very distant from the atropinized area. These results support the view of cholinergic synaptic transmission within a circumscribed hypogenic circuit extending from the forebrain to the limbic midbrain area.

Unidad de Investigaciones Cerebrales
Mexico City, Mexico

- 1546 Malhotra, C. L. & Prasad, K. The effect of intra(cerebro)ventricular reserpine on the acetylcholine content of the heart, ileum and hypothalamus of the dog. *British Journal of Pharmacology and Chemotherapy*, 21(2):355-360, 1963.

This study was designed to find out whether the predominant peripheral parasympathetic effects of reserpine on the heart, intestinal motility, and pupillary size, and also the increase in the acetylcholine content of the sino-atrial node and the ileum were central or peripheral in origin. The effect of injection of reserpine into the cerebral ventricles on the acetylcholine contents of the sino-atrial node, ileum, and hypothalamus of the dog was studied in 10 dogs. Another group of five dogs served as a control. The effect of i.v. administration of reserpine, in the same dose as given intracerebroventricularly, was also studied on the acetylcholine content of these tissues in five dogs. General sedation, bradycardia, miosis, salivation, emesis, and purgation were looked for. Tissues were removed 1 hour after administration of reserpine for estimation of acetylcholine content, which was increased in all the tissues studied. The increase in the peripheral tissues was greater than in the hypothalamus. The increase in the acetylcholine content was not quantitatively related to the other effects of reserpine. The increase in the acetylcholine content of the sino-atrial node and the ileum and also the peripheral effects observed on intracerebroventricular administration of reserpine can be attributed to its central action. With the same dose of reserpine given i.v., the acetylcholine content of the sino-atrial node was significantly increased, but that of the hypothalamus and ileum was not.

Lady Hardinge Medical College
New Delhi, India

- 1547 Stafford, Anne. Potentiation of some catechol amines by phenoxybenzamine, guanethidine and cocaine. *British Journal of Pharmacology and Chemotherapy*, 21(2): 361-367, 1963.

In rabbit isolated atria, cocaine (0.5 µg/ml), guanethidine (0.4 µg/ml), and phenoxybenzamine (0.1 µg/ml and 0.3 µg/ml) increased the changes in rate and force of contractions caused by noradrenaline (0.02 µg to 2 µg), and adrenaline (0.1 µg to 5 µg), but did not potentiate isoprenaline (0.002 µg to 0.02 µg). The most likely explanation for this result is that the drugs inter-

fere with one of the mechanisms in the heart by which noradrenaline and adrenaline, but not isoprenaline, are inactivated; a probable mechanism would be the uptake of noradrenaline into storage sites in the tissue. Cocaine, guanethidine, and phenoxybenzamine did not potentiate noradrenaline and adrenaline acting on the rabbit isolated duodenum and the rat uterus.

The London Hospital Medical College
London, England

- 1548 Sherman, H., Fiasconaro, J. E., & Grundfest, H. Laboratory evaluation of analgetic effectiveness in human subjects. *Experimental Neurology*, 7(6):435-456, 1963.

The object of this study was to devise a satisfactory method for eliciting and measuring pain in man. A method based on electrophysiological principles is described for evaluating actions of analgesic agents in controlled tests using electrical stimulation of the dental pulp. Some of the tests depended upon use of subjects who were selected according to an objective criterion of responsiveness to painful stimuli, characterized by digital plethysmography. Other subjects were selected on the basis of an observed correlation between the plethysmographic findings and the subjective reactions of different individuals to the electrical stimuli. About 25% of the individuals tested were rejected because of erratic threshold to electrical stimulation in a preliminary test, or both. None of the individuals chosen by either criterion for subsequent testing reacted to administration of placebo. About two-thirds of the group responded with marked elevations of electrical threshold to orally administered acetylsalicylic acid (1.8 gm) or codeine (30 mg). The elevations caused by codeine were about three times as large as those induced by the acetylsalicylic acid. Twenty-five percent of those examined proved refractory to 1.8 gm acetylsalicylic acid, and to 30 mg codeine. The present findings are in accord with clinical experience, but there are discrepancies with statistical evaluations using clinical material.

Columbia University
New York, New York

1549 Pershin, G. N. & Nesvad'ba, V. V.

Study of the monoaminoxidase activity of mycobacteria B₅. Bulletin of Experimental Biology and Medicine, 56(8):904-907, 1963.

The acetone preparation obtained from the acid-fast saprophyte, B₅, has significant monoaminoxidase activity. Maximum activity of the enzyme was observed at pH of 8 to 10; lowering the pH to 6 or raising it to 12 decreased the activity by a factor of approximately 2. Activity changed, depending on the concentration of the enzymatic material, maximum activity being obtained with a concentration of 40 to 50 mg/ml. At 37° C and the optimal pH of the medium, of the substrate (thiamine) concentration, and of the acetone B₅ mycobacteria preparation, the enzymatic process reached its equilibrium in 16 to 20 hours. Monoaminoxidase activity was lost after the B₅ acetone preparation suspension was heated for 5 minutes in a water bath at 65° C. The 8-phenylisopropylhydrazine suppresses monoaminoxidase activity more intensely than does ipraside (1-isonicotinoyl-2-isopropylhydrazine). It is therefore concluded that the monoaminoxidase of the B₅ bacteria is similar in its properties to the monoaminoxidases of animal origin.

Chemico-Pharmaceutical Institute
Moscow, U.S.S.R.

1550 Dlabáč, A. & Trčka, V. *Centrální tlumivý účinek některých nových látek ze skupiny reserpinu.* (The central inhibitory effect of some new drugs of reserpine group.) *Activitas Nervosa Superior*, 5:164, 1963.

A pharmacological study was made of the central inhibitory effect of hypotensive drugs, similar to reserpine, that had been synthesized by two research groups. Drug efficacy was evaluated on the basis of dosage of the test drug necessary to produce a standard response in thiopental narcosis and ptosis of the eyelid in Rhesus monkeys and in mice. It was found that ethoxyl substitution on the trimethoxybenzoyl portion of the reserpine molecule leads to an increase in sedative activity (homoreserpine and bishomoreserpine). Substitution in the para position of this portion of the molecule (the methoxyl-methyl, or carbethoxyl group) results in a relatively small decrease in efficacy (4'-desmethoxy-4'-methylreserpine, and syrosingopine). Bihomosyrosingopine and dl-deserpidine were found to possess equal sedative activity. Phenoxyacetylreserpate, in which the benzene core has been removed

from the E ring, has less and shorter inhibitory effect. Mescaline analogs of despyroloisoreserpine had only slightly reduced excitatory effect. Despite considerable changes at various points on the reserpine molecule, no qualitative differences were ascertained among the reserpoids synthesized, although quantitative comparisons with reserpine effect could be made.

Research Institute for Pharmacology and Biochemistry
Prague, Czechoslovakia

1551 Myers, Robert D. Alcohol consumption in rats: Effects of intracranial injections of ethanol. *Science*, 142(3589):240-241, 1963.

Preference for ethanol was positively related to the amount injected intracranially over a period of time. In addition, the persistence of the preference for over 2 weeks after cessation of infusion tends to support the hypothesis that alteration to the CNS may be permanent. A new biochemical theory of alcoholism may have to be evolved that will place its primary focus on a metabolic aberration of the CNS. Five groups of from 2 to 4 adult male rats (Colgate strain) were stereotactically implanted with unilateral 23-gauge syringe needle cannulae, after which, intracranial infusion was initiated. Schedules were maintained in which 1μl to 3μl of 5% and 10% ethanol were administered at a rate of one infusion every 15 minutes throughout a 10-day period. Each rat received 1,000 intraventricular microinjections. Subsequently, 6 rats previously unexposed to ethanol were subjected for 5 days to infusion of 2μl of 10% ethanol every 15 minutes and to offerings of water. Preference thresholds were determined. Retesting after 5 days of cessation was followed by systematic administration of meprobamate and hydroxyphenamate to determine whether ataractic drug treatment would reduce the preference, which it did not.

Colgate University
Hamilton, New York

1552 Udenfriend, S. & Zaltzman, P. *Nor-pinephrine and 3,4-dihydroxyphenethylamine turnover in guinea pig brain in vivo.* *Science*, 142(3590):394-396, 1963.

It was possible to label the brain catecholamines by administering C¹⁴-labeled tyrosine or H³-labeled 3,4-dehydroxyphenylalanine of high specific activity and 3,4-dehydroxy-

phenylalanine of high specific activity, and to estimate the turnover rate from the rate of disappearance of label from the individual catecholamines. One hundred microcuries of tyrosine-3- C^{14} or 200 microcuries of H^3 -labeled DOPA were administered i.p. to adult guinea pigs weighing 200 to 250 g. At various time intervals, individual animals were killed and decapitated. The brain was removed and homogenized in 10 ml of 5% tri-chloroacetic acid. The homogenate was centrifuged, and catecholamines were isolated by absorption and elution from alumina. One cannot really calculate turnover values for the catecholamines since the tyrosine was at all times more highly labeled than the products. Nevertheless, half-lives of a least 3 to 4 hours can be estimated for both norepinephrine and dopamine. It is indicated that norepinephrine synthesis is a rapid process in the CNS, and support is given to concepts concerning a neurohumoral function in the brain.

National Institutes of Health
Bethesda 14, Maryland

- 1553 Ansell, G. B. & Marshall, Elizabeth F. Some effects of chlorpromazine on brain phospholipid metabolism—I. Effects of the drug on phospholipids *in vivo* and *in vitro*. *Journal of Neurochemistry*, 10(12): 875-881, 1963.

Single injections of chlorpromazine (10 mg/kg body weight) into 3 week-old animals elicited a response different from that obtained with chronic injections. The uptake of P^{32} into phosphatidylcholine and phosphatidylinositol compared with the inhibition of uptake into these phospholipids after chronic administration, but the uptake into phosphatidic acid and phosphatidylserine was only slightly affected. This might well indicate that there is no cumulative effect of the drug on this process. Further investigations were made using animals 10 days and 3 months old. The exchange of P^{32} in phosphatidylserine was more significantly depressed in the young rat, whereas the exchange in the phosphatidylcholine was no more sensitive in either. Low concentrations of chlorpromazine (10^{-4} M) stimulated P^{32} uptake into phosphatidic acid and depressed that into phosphatidylserine in brain slices from adult animals.

The Medical School
Birmingham, England

- 1554 Poulson, Evelyn, Robson, J. M., & Sullivan, F. M. Teratogenic effect of 5-hydroxytryptamine in mice. *Science*, 141(3582):717-718, 1963.

A nonpure line of white mice was used. They were divided into three groups. Groups 1 and 2 received on s.c. injection of 2.0 mg of synthetic 5-hydroxytryptamine creatine sulfate. Progesterone in oil (2.0 mg) was also injected s.c. in Group 2 to confirm the failure of progesterone to reverse the lethal effect of 5HT. Mice in Group 3 received one s.c. injection of 0.5 mg of 5HT. This lower dose is effective in interrupting pregnancy with no obvious toxic effects except for transient diarrhea. By the 10th day, most of the fetuses in Groups 1 and 2 had been killed, but some 70% of the fetuses survived from Group 3. A high incidence of fetal abnormalities was found in surviving fetuses from all groups. Eyes, limbs, and tails were most frequently affected. These results show that 5HT is a powerful teratogen. It has not been established that the mode of action could be by interference with placental function.

Guy's Hospital Medical School
London, S.E.1, England

- 1555 Friedman, Alexander H., Aylesworth, Robert J., & Friedman, Gertrud. Tremorine: Its effect on amines of the central nervous system. *Science*, 141(3586): 1188-1190, 1963.

Because tremorine produced acute Parkinson-like states in laboratory animals, an experiment was performed to determine whether the compound affected the amines of the CNS. Tremorine was administered i.p., 15 to 20 mg/kg of body weight; controls either received saline or were untreated. In the rat, mouse, and guinea pig, a significant decrease occurred in the concentration of norepinephrine in the brain stem. A week after bilateral adrenalectomy, 20 mg/kg of tremorine decreased the concentration of catecholamines by 31.4% in 90 minutes (15.5% in unoperated animals). The depletion of norepinephrine increases, concentration of 5-hydroxytryptamine was unaltered, and tremor diminished, suggesting that tremorine tremor involves both central and peripheral mechanisms, and that those in the periphery modulate those in the CNS by feedback.

University of Wisconsin Medical School
Madison, Wisconsin

- 1556 v. Euler, U. S., Stjärne, L., & Lishajko, F. **Uptake of radioactively labeled dl-catecholamines in isolated adrenergic nerve granules with and without reserpine.** *Life Sciences*, 2(11):878-885, 1963.

On incubation with radioactively labeled catecholamines, adrenergic nerve granules take up an amount of extragranular amines exceeding fluorimetrically determined uptake. Spontaneous loss of amines during incubation in vitro in a noradrenaline-free medium is due to an outward flux in excess of the inward flux. When adrenaline is added to the external medium in a concentration of 10 µg/ml to 20 µg/ml, it successfully competes for available binding sites with the endogenous amines continuously released. There is evidence that reserpine strongly inhibits the outward flow of endogenous amines. Reserpine may be bound to some vital site even at 0° C, and may act by interfering with the amines at a physico-chemical level. Spontaneous decrease in intragranular catecholamines during incubation in vitro is not as efficiently counteracted by addition of dl-noradrenaline or dl-adrenaline, even at twice the concentration, as by the pure 1-form. This implies stereospecificity in the uptake mechanism for adrenal medullary granules and for nerve granules.

Karolinska Institutet
Stockholm, Sweden

- 1557 Andén, Nils-Erik, Carlsson, Arvid, & Waldeck, Bertil. **Reserpine-resistant uptake mechanisms of noradrenaline in tissues.** *Life Sciences*, 2(12):889-894, 1963.

Male hooded rats, weighing about 250 g, were used. Injection was made of 1 µg/kg body weight tritiated noradrenaline into one external jugular vein. Reserpine, the monoamine oxidase inhibitor nialamide, and the catechol-O-methyl transferase inhibitor 2-(3,4-dehydroxyphenyl)-pentanoyl amide were given 18 hours, 2 hours, and 0.5 hours, respectively, before the injection of tritiated noradrenaline. The animals were sacrificed 30 minutes later, the submaxillary glands removed and weighed, and their contents of tritiated noradrenaline and tritiated normetanephrine were determined. The uptake of tritiated noradrenaline in the denervated submaxillary gland was 10% that in the intact gland in control animals. Pretreatment with reserpine blocked uptake in the intake gland so that difference between the glands disappeared. In reserpine-

treated animals where monoamineoxidase was inhibited by nialimide, tritiated noradrenaline uptake increased in the intact gland, but was unchanged in the denervated. In animals pretreated with reserpine, nialimide, and 2-(3,4-dehydroxyphenyl)-pentanoyl amide, the uptake of tritiated noradrenaline increased in both intact and denervated glands. The possibility should be considered that the adrenergic receptors of the effector cells are involved. Formation of tritiated normetanephrine was efficiently blocked by 2-(3,4-dehydroxyphenyl)-pentanoyl amide.

University of Göteborg
Göteborg, Sweden

- 1558 Burn, J. H. & Froede, H. **Action of substances which block sympathetic postganglionic nervous transmission.** *British Journal of Pharmacology and Chemotherapy*, 20(2):378-387, 1963.

Nine compounds block responses to sympathetic post ganglionic stimulation; seven of these are onium compounds. They are, however, mon-onium compounds so they can enter the postganglionic fiber, which bis-onium compounds like hexamethonium and decamethonium may not be able to do. Since these mon-onium compounds have some blocking action at neuromuscular junctions and at sympathetic ganglia, their block of postganglionic transmission may be essentially similar to that by hexamethonium at ganglia and decamethonium at neuromuscular junctions. Acetylcholine releases noradrenaline from sympathetic postganglionic terminations, and xylocholine and bretylium block this release in the vessels of the rabbit ear and in the rabbit isolated atria.

Washington University School of Medicine
St. Louis, Missouri

- 1559 Harry, J. **Action of drugs on the circular muscle strip from the guinea-pig isolated ileum.** *British Journal of Pharmacology and Chemotherapy*, 20(3):399-417, 1963.

The circular muscle strip was prepared to examine drug action on the circular muscle of the guinea-pig isolated intestine. Normally insensitive to drugs acting on autonomic effector tissues, each strip was pretreated with the anticholinesterase NN-diisopropylphosphorodiamidic fluoride (mipaflox). Strip contractions by 5-hydroxytryptamine,

histamine, and nicotine were abolished by procaine, botulinum toxin (Type A), morphine and hemicholinium; acetylcholine and methacholine actions were unaffected. Atropine and hyoscine abolished strip contractions in response to drugs. Hexamethonium specifically antagonized nicotine; tissue was desensitized to 5-hydroxytryptamine, and mepyramine antagonized histamine action. Nicotine, histamine, and 5-hydroxytryptamine stimulate specific receptor sites within intramural nerve plexuses of the isolated ileum. Botulinum toxin (Type A), morphine, or hemicholinium more readily depressed circular muscle strip contractions due to histamine or nicotine than those due to 5-hydroxytryptamine.

King's College
London, W.E.2, England

- 1560 Giarman, N. J. & Schmidt, K. F.
Some neurochemical aspects of the depressant action of γ -butyrolactone on the central nervous system. British Journal of Pharmacology and Chemotherapy, 20(3):563-568, 1963.

Acetylcholine in mice and rats was the only compound changed in amount by the depressant action of γ -butyrolactone on the brain. In the cerebral cortex, levels of acetylcholine were increased by γ -butyrolactone at a time course correlative with the development of the animal's depressed state, the peak of increase occurring at 15 minutes when central nervous depression is deepest. It is indirectly shown that in the midbrain and brain stem, change in acetylcholine level induced by γ -butyrolactone is sharply localized in an area of the mesencephalon containing the corpora quadrigemina.

Yale University School of Medicine
New Haven, Connecticut

- 1561 Boyd, Helen, Burnstock, G., Campbell, G., Jowett, Alison, O'Shea, Judith, & Wood, Margaret. **Cholinergic blocking action of adrenergic blocking agents in the pharmacological analysis of autonomic innervation.** British Journal of Pharmacology and Chemotherapy, 20(3):418-435, 1963.

Adrenergic blocking agents (tolazoline, phentolamine, piperoxan, yohimbine, phenoxybenzamine, bretylium, and guanethidine) were studied for antiacetylcholine activities in the guinea-pig rectum and toad bladder. In

preparations sensitive to eserine, potentiation or block of responses to acetylcholine and to cholinergic nerve stimulation occurred with different concentrations. Eserine did not potentiate toad-bladder responses to acetylcholine. Results of blocking on guinea-pig rectum pretreated with dyflos were similar qualitatively. Phenoxybenzamine often completely blocked responses both to added acetylcholine and cholinergic nerve stimulation in concentrations less than those needed to block adrenergic nerves; guanethidine and piperoxan showed strong cholinergic blocking; bretylium, yohimbine, tolazoline, and phentolamine were less potent. Adrenergic blocking agents cannot be used to distinguish conclusively between adrenergic and cholinergic nerves. Substances released upon nerve stimulation must be subjected to specific biochemical techniques or bioassay for reliable analysis of autonomic innervation.

University of Melbourne
Victoria, Australia

- 1562 Goldstein, Menek & Gerber, Heinz.
Phenolic alcohols in the brain after administration of DOPA- C^{14} or dopamine- C^{14} . Life Sciences, 2(2):97-100, 1963.

White male rats, weighing approximately 100 g, were given dl-DOPA-2- C^{14} with specific activity of 0.67 mc/mmol (20 mg/kg body weight, i.p.). In some experiments, the animals were pretreated with calcium carbamide. When dopamine- C^{14} was administered, 3-methoxy-4-hydroxy-phenylethanol (MHPE) was found in the blood as well as in the central nervous system (CNS), whereas 3-methoxy-4-hydroxyphenylacetic acid (HVA) was found only in the blood. This indicates that MHPE accumulates in the CNS through uptake from the blood, and that HVA is synthesized in the CNS. Almost no MHPE- C^{14} was detected in the blood; the levels in the brain were higher. This suggests that phenolic alcohol was formed in the CNS and that O-methylation occurs in the brain. Other amines (norepinephrine, epinephrine, tryptamine, and mesocaine) are metabolized to the corresponding phenolic alcohols; it is possible they are also formed and accumulated in the CNS. The phenolic alcohols were found in the brain as conjugates.

New York University
New York 16, New York

- 1563 Roos, Björn-Erik & Werdinius, Bengt.
The effect of α -methyldopa on the metabolism of 5-hydroxytryptamine in brain. Life Sciences, 2(2):92-96, 1963.

The α -methyldopa was given intravenously to rabbits, and the animals were killed, after various intervals, by injection of air. At regular intervals, untreated animals were taken for determination of normal values of 5HT (5-hydroxytryptamine) and 5HIAA (5-hydroxyindoleacetic acid). The brain level of 5HT rapidly decreased after a single intravenous injection of α -methyldopa in a dose of 200 mg/kg; it reached its lowest value 3 hours after injection. After 24 hours, the 5HT was normal again. It required about 12 hours for the 5HIAA value to reach half the normal, since it appeared to decrease at a slower rate. After 24 hours, the 5HIAA value was about 75% of normal. The most reasonable explanation of the simultaneous decrease in 5HT and 5HIAA levels in brain appeared to be that α -methyldopa caused an inhibition of synthesis of 5HT in brain.

University of Göteborg
Göteborg, Sweden

- 1564 Lal, H., Ginocchio, S., & Shefner, A. The effect of α -methyl-3,4-dihydroxyphenylalanine (methyl-dopa) and α -methyl-meta-tyrosine (α -MMT) on amphetamine toxicity. Life Sciences, 2(3):190-192, 1963.

An aqueous solution of d-amphetamine sulfate was administered i.p. to male, random-bred, Swiss albino mice, pretreated with l- α -methyl-3,4-dihydroxyphenylalanine or dl- α -methyl-meta-tyrosine. The increased toxicity of amphetamine in aggregated mice was partially prevented by this pretreatment. Methyl-dopa and α -methyl-meta-tyrosine decrease the levels of serotonin, dopamine, and norepinephrine in guinea pigs (heart and brain). The effect of α -methyl-meta-tyrosine on brain amines has been confirmed in mice. In the present study, these agents were found to protect against the increased toxicity of amphetamine.

Illinois Institute of Technology
Chicago 16, Illinois

- 1565 Bovet-Nitti, F., Bignami, G., & Bovet, D. Antihistamine drugs on rat pregnancy: Effects of pyrilamine and meclizine. Life Sciences, 2(5):303-310, 1963.

In the first of two series of trials, Wistar Glaxo rats were killed within 24 hours after parturition: in the second series, Wistar S.

M. rats were killed on the 21st day of pregnancy. Pyrilamine maleate was administered both by gavage and i.m., in water solution in doses equal to about 1/6 to 1/8 of the convulsant dose. Meclizine was administered only by gavage as a suspension. Pyrilamine administered in the early stages of pregnancy in the rat caused an increase in the frequency of implantation anomalies and several toxic effects in the last stages of pregnancy. Meclizine had virtually no effects.

Istituto Superiore di Sanità
Rome, Italy

- 1566 Podlesnaya, A.I. Paramion contraction of the dorsal muscle of the leech during the action of anticholinesterase drugs. Bulletin of Experimental Biology and Medicine, 55(5):546-549, 1963.

A segment of the dorsal muscle of the leech was placed in a vessel with Ringer's solution for 2 hours after isolation while oxygen was bubbled through. Ninety-four experiments with 110 tests were performed. High concentrations of paramion relaxed the acetylcholine contracture of the muscle. Low doses may cause contracture after pretreatment of the muscle with eserine or prostigmine, but not with nivalin. This suggests that, depending on its concentration, paramion may act both in the manner of d-tubocurarine (blocking cholinergic structures) and of decamethonium (causing persistent depolarization). Consequently, in small doses, paramion potentiates the action of acetylcholine, and in large doses, depresses it.

Institute of Experimental Medicine
Leningrad, U.S.S.R.

- 1567 Day, Margaret & Vane, J.R. An analysis of the direct and indirect actions of drugs on the isolated guinea-pig ileum. British Journal of Pharmacology and Chemotherapy, 20(1):150-170, 1963.

Anoxia or cooling abolished the response to single shocks. Under these conditions, the response of the ileum to histamine, acetylcholine, and bradykinin was barely affected, indicating direct action on muscle fibers. Effects of nicotine, tetramethylammonium, dimethylphenylpiperazinium, and 5HT were reduced to various degrees, indicating their main actions to be indirect through cholinergic nerve-fiber stimulation. Exposure of the ileum to hyoscine and phenoxybenzamine showed that direct actions of nicotine and

tetramethylammonium were not only on acetylcholine receptors but also on receptors insensitive to hyoscine but sensitive to phenoxybenzamine. The main action of 5HT was on nervous elements; treatment with phenoxybenzamine produced a higher dose ratio for 5HT than did treatment with morphine. It is believed that: (1) receptors sensitive to morphine are in nervous tissue, whereas those sensitive to phenoxybenzamine are in smooth muscle. (2) Morphine is only a partial antagonist of 5HT receptors in nervous tissue, whereas phenoxybenzamine antagonizes more 5HT receptors than those in smooth muscle.

Royal College of Surgeons of England
London W.C.2, England

- 1568 Mettler, Fred A. & Stern, Gerald M.
Observations on the toxic effects of yellow star thistle. *Journal of Neuropathology and Experimental Neurology*, 22(1):164-169, 1963.

Mice, rats, and monkeys were tested for toxic effects of yellow star thistle. Lesions comparable to those found in horses fed on star thistles could not be established in the tested animals. The primate seems unsusceptible to chronic ingestion on the plant or gastric instillation of its extract, although test conditions were different from those for horses, since monkeys cannot be kept alive on a diet limited to the plant. All extracts of the plant, whether made with water, alcohol, or a dilute aqueous solution of alcohol, are toxic for mice, rats, and monkeys if injected s.c. in large enough doses. Smaller doses produce no neurologic lesions.

Columbia University
New York, New York

- 1569 Ramwell, P. W. & Shaw, Jane E. **The spontaneous and evoked release of non-cholinergic substances from the cerebral cortex of cats.** *Life Sciences*, 2(6):419-426, 1963.

Cats were anesthetized with sodium pentobarbitone (25mg/kg) i.p. Direct transcallosal and forepaw stimulation were performed by means of a unipolar electrode, at 0.25 to 100 stimuli/second. Perfusates of the cortex were digested with chymotrypsin (1mg/ml) at 37°C for 30 minutes after which the enzyme was inactivated by boiling for 10 minutes. Using syntocinon, bradykinin, or

other pharmacologically active polypeptides as substrates, the enzyme's activity was always tested. Stimulation of the cortex for 10 minutes by means of a unipolar electrode inserted into the pool of de Jalon's solution markedly increased the release of oxytocic material, which was only slightly elevated by subsequent contralateral forepaw stimulation at 100 stimuli/second. Increased release of active material into the superfusate of the cortex was also elicited by use of the analeptic drugs picrotoxin and leptazol. With this stimulation, a variable proportion of the released active material was found to be destroyed on incubation with chymotrypsin.

The Medical School
Birmingham 15, England

- 1570 Lavery, R. **The influence of cold environmental temperature and histamine treatment on the effect of reserpine in the rat.** *Journal of Neurochemistry*, 10(3):151-154, 1963.

Possible effects of cold and of histamine on the depletion of endogenous brain 5HT by reserpine were investigated in female Wistar albino rats (110 to 150 g). The rats were decapitated 4 hours after s.c. reserpine injections, and the 5HT contents extracted from brain tissues, excluding the olfactory lobes and cerebellum, were estimated spectrofluorometrically. Eight rats were exposed to temperatures of from 2° to 5° C for 4 hours before and after injections of reserpine (1 mg/kg). All rats showed diarrhea. Eight rats were exposed to a temperature of 3° ± ½° C for 20 hours before and 4 hours after injections of reserpine (2.5 mg/kg). Their mean rectal temperature fell 0.5° C. Four rats were fasted overnight, and placed in a cold room at 2° C for 4 hours before and after injections of reserpine (2.5 mg/kg). Their mean rectal temperature fell 3.4° C. In both experiments, rectal temperatures were taken before injection and before decapitation. Results of these three experiments indicated that exposure to a cold environment, with or without fasting, did not prevent the sedation caused by reserpine and only occasionally, and to a very small extent, antagonized the decrease in brain 5HT. Histamine (20 mg acid phosphate salt/kg) was injected into rats along with and 1 hour following the same dosage of reserpine. All rats were decapitated 2 hours after receiving reserpine. No difference in the 5HT de-

pletion or sedation was observed in the 10 control rats given reserpine and the 10 rats given reserpine and histamine.

A.R.C. Institute of Animal Physiology
Babraham, Cambridge, England

- 1571 Scotto, P., Monaco, P., Scardi, V., & Bonavita, V. **Neurochemical studies with l-cycloserine, a central depressant agent.** *Journal of Neurochemistry*, 10(11): 831-839, 1963.

The effect of l-Cycloserine, A CNS depressant, on the GABA level in mouse (female albino) and cat brain was investigated both in vivo and in vitro. l-Cycloserine (300 mg/kg) injected i.p. into mice resulted in a GABA level elevation in the whole brain. The maximum level was obtained at 2 hours, followed by a fast return to the baseline between the fifth and seventh hour. The percentage activity of γ -aminobutyric- α -ketoglutaric transaminase (ABAT) was as low as 25% of the control level at the second hour after injection, glutamic decarboxylase (GDC) exhibited a slighter decrease. l-Cycloserine (125 mg/kg) injected i.p. in cats resulted in variations in the elevation of GABA levels in different parts of the brain, the greatest increase being in the brain stem. An i.p. injection of an equimolar amount of pyridoxal hydrochloride 3 hours after l-cycloserine caused a complete reversal of the GABA levels to their baseline values. In vitro studies on l-cycloserine inhibition of ABAT and GDC indicated a maximum activity of ABAT at a pH of approximately 8.0 and of GDC at pH values of 6.9 to 7.0. Also, l-cycloserine was found to be a more powerful inhibitor of ABAT than the d-isomer and GDC was found to be less sensitive to both cycloserine isomers than ABAT. In a preliminary experiment an i.v. injection of pyridoxal hydrochloride (100 mg/kg) or its phosphate into intact cats injected i.v. with l-cycloserine (50 mg/kg) caused behavioral and electrophysiological normalization and also the return of elevated GABA and inhibited ABAT to their normal values.

Department of Neurology and Department of Organic Chemistry
University of Naples, Naples, Italy

- 1572 Tews, Jean Kring, Carter, Samuel H., Roa, P. Dante, & Stone, William E. **Free amino acids and related compounds in dog brain: Post-mortem and anoxic changes, effects of ammonium chloride infusion, and levels during seizures induced by picrotoxin and by pentylenetetrazol.** *Journal of Neurochemistry*, 10(9):641-653, 1963.

Cerebral tissue from adult male dogs under morphine analgesia was analyzed for free amino acids and related constituents. Amino-acid separation was by ion-exchange chromatography. The chemical pattern found in excised tissue 20 to 23 minutes post-mortem was compared with that in tissue obtained by fixation in vivo with liquid air. Alanine showed the greatest response to lack of oxygen during the administration of 4.5% oxygen for 12 to 13 minutes and under post-mortem conditions. GABA also increased under anoxia and post-mortem conditions. Glutamic acid, leucine, and tyrosine increased significantly during anoxia; no significant change in ammonia was noted. Aspartic acid, methionine, and cystathionine decreased. Other measured nitrogenous constituents remained at normal levels. Under post-mortem conditions, both ammonia and lactic acid showed large increases. Changes in cerebral levels of a number of free amino acids and related substances, including citric acid, during anoxia or post-mortem conditions were insignificant. Depression of cortical electrical activity was generally observed after an infusion of buffered ammonium chloride solutions for 10 and 45 minutes, although in one animal a seizure developed. The cerebral-ammonia level was greatly increased in every instance; it was highest in the animal having a seizure. Glutamine showed a minimal change at 10 minutes but was greatly increased at 45 minutes. Alanine showed a large increase, and lactic acid also increased. Histidine showed a small but significant increase. Aspartic acid and valine decreased. Urea levels were generally high but variable. During picrotoxin seizures, the only significant change was a slight decrease in aspartic acid. In pentylenetetrazol seizures, alanine and ammonia increased; glutamic acid decreased slightly.

University of Wisconsin Medical School
Madison, Wisconsin

- 1573 Pellegrino de Iraldi, Amanda, Zieher, L. M., & De Robertis, E. **The 5-hydroxytryptamine content and synthesis of normal and denervated pineal gland.** *Life Sciences*, 2(9):691-696, 1963.

A study was made of the nature plurivesicular material found in nerve fibers and endings within the pineal gland of the rat as

well as the localization of 5HT within the pineal gland. Groups of 6 to 20 adult white rats were used for each experiment. In one-half of the animals, the cervical ganglia were bilaterally extirpated, and the 5HT content was measured between 5 and 30 days after denervation. Two pools of 5HT of similar size were found in the nerves and nerve endings and in the parenchymal cells. To study the synthesis of 5HT, groups of normal and denervated rats were injected i.v. with 25 mg/kg 5HTP and sacrificed after 30 minutes. The mean of 55 determinations of the normal 5HT content of rat pineal showed a concentration of 11.14/g 5HT, which is more than 30 times greater than that of the whole rat brain. The 5HT content of the pineal decreases 73%, 5 days after denervation, and stabilizes at about 50% of the control level after 10 days. With i.v. injection of 5HTP, the pineal content of 5HT increases at different rates in the normal pineal and in the brain, and 5HT formation is reduced to about one-fifth of normal in the denervated glands. There is practically no uptake of 5HT by the normal pineal gland and by the brain, although there is some increase above the control level in the denervated gland.

Institute of General Anatomy and Embryology
Buenos Aires, Argentina

- 1574 Jori, A., Bonaccorsi, A., Valzelli, L., & Garattini, S. **New orally active monoamine oxidase (MAO) inhibitors.** *Life Sciences* 2(8):611-617, 1963.

After preliminary evaluation of 24 compounds of a series of mono- and bi-substituted hydrazines attached to indole, benzyl, and phenyl groups, four compounds (L7, T1, T3, and T8) were selected for comparison of MAO inhibiting activities with phenelzine and pheniprazine. The test subjects were female Sprague--Dawley rats with an average weight of 150 g. The in vivo evaluation of MAO inhibition was carried out by the tryptamine (10 mg/kg, i.v.) and reserpine (2.5 mg/kg, i.p.) tests. The MAO was determined in vitro by measuring the oxidation of kynuramine in brain and liver homogenates from rats pretreated with the MAO inhibitors. Serotonin and noradrenaline levels in brain and spleen were measured according to the method of Shore. Toxicity was determined from the mortality at 72 hours after a single oral administration. Compounds T3, T8, and L7 blocked MAO activity more effectively than phenelzine and pheniprazine when given p.o. at a dosage close to the computed ED₅₀. Administration of all four test compounds p.o. at a dosage equal to one-tenth of the LD₅₀

resulted in an increase in tissue amines 4 hours later. Brain serotonin increased about 2 hours after p.o. administration and persisted for more than 72 hours. The T3 compound showed a much greater therapeutic index than pheniprazine.

Mario Negri Institute of
Pharmacological Research
Milan, Italy

- 1575 Maling, H. M., Wakabayashi, M., & Horning, M. G. **Alterations in hepatic lipid biosynthetic pathways after ethanol, ethionine and carbon tetrachloride.** *Advances in Enzyme Regulation*, 1:247-257, 1963.

Sprague--Dawley rats, weighing from 150 to 200 g, were fasted overnight, and given ethanol (6 g/kg) in water or carbon tetrachloride (1.5 ml/kg) in mineral oil; both were administered by means of a stomach tube. Ethionine was injected i.p. in 3 doses of 250 mg/kg each, 2 ½ hours apart. Albumin-bound 1-C¹⁴-palmitate was incubated with the homogenate supernatant of liver of the rats. Results showed that administration of ethanol, carbon tetrachloride, or ethionine to rats increases the incorporation of 1-C¹⁴-palmitate in triglycerides and decreases incorporation into phospholipids. The liver homogenates from both treated and untreated hypophysectomized rats showed less palmitate in the triglycerides and more in the phospholipids than those from intact rats, indicating that the pituitary is essential for development of a fatty liver after ethanol, but that other factors also are probably involved in fatty liver after ethionine or carbon tetrachloride. Liver homogenates from female rats, either treated or untreated with ethionine, showed more radioactive palmitate in the triglycerides than those from male rats. Addition of cytidine-5'-diphosphate choline in vitro prevented the alteration of incorporation pattern usually seen in homogenates from ethanol treated rats, but not in homogenates from rats treated with carbon tetrachloride.

National Heart Institute
National Institutes of Health
Bethesda, Maryland

1576 Gillette, James R. **Factors that affect the stimulation of the microsomal drug enzymes induced by foreign compounds.** *Advances in Enzyme Regulation*, 1: 215-223, 1963.

The works of many authors on the stimulation by a wide variety of foreign compounds of enzymes of the smooth microsomes of liver that catalyze the oxidation and reduction of drugs show that this stimulation acts through at least three different mechanisms. These mechanisms are: by anabolic steroids (studies made with testosterone, testosterone, testosterone propionate, methyltestosterone, androstenedione, 19-nortestosterone and 4-chloro-19-nortestosterone acetate), by polycyclic hydrocarbons (3-methylcholantrene, and 3,4-benzpyrene), and by phenobarbital and other long-lasting barbiturates. Studies made with prednisolone, cortisone, and hydrocortisone suggest that adrenal hormones increase the effectiveness of the anabolic steroids in stimulating the activity of drug metabolizing microsomal enzymes.

National Heart Institute
Bethesda, Maryland

1577 Smol'nikova, N. M. **Analysis of the depressant action of d,l- and d-cycloserine on the central nervous system.** *Bulletin of Experimental Biology and Medicine*, 55(3):293-295, 1963.

The effects of d,l-cycloserine and d-cycloserine on the CNS were studied further by combining them with certain drugs depressing the nervous system. The subjects were 200 albino mice weighing 18 to 20 g. Three groups of mice were tested with each of the four depressants: one group with the d,l-isomer, one with the d-isomer, and one without any cycloserine. Groups of about 10 mice apiece were injected i.p. with chloral hydrate (300 mg/kg), ethaminal (20 mg/kg), or thiopental (50 mg/kg); groups of 30 mice apiece were injected i.p. with luminal (100 g/kg). Cycloserine was given orally in a dose of 50 mg/kg 2 hours before injection of chloral hydrate and the barbiturates. The duration and depth of depression were estimated in controls and after the preliminary injection of cycloserine. The results showed that d,l-cycloserine potentiated the action of the four depressants. The potentiating effect of d-cycloserine, however, was observed only in respect to ethaminal and thiopental and was much weaker.

Institute of Pharmacology and Chemotherapy
of the AMN SSSR
Moscow, Russia

1578 Maslov, S. P. & Ivashkina, I. N. **Amytal resistance in animals to cold, and some features peculiar to the mechanism of its narcotic action.** *Bulletin of Experimental Biology and Medicine*, 55(6):656-659, 1963.

The possibility that amytal resistance in the respiration of animals in a cold environment can be used to control a disturbance in oxidation and phosphorylation *in vivo* was tested on white adult female mice (26 g) adapted to a temperature of -15°C for a period of less than 10 hours at a time. There were 25 control and 25 adapted-to-cold mice used to determine the action of amytal on gas exchange and 66 mice used to study the narcotic action of amytal. The animals were injected on the day after the last chilling with 115 mg/kg sodium amytal s.c. in a 0.6% aqueous solution. Prior to this, the total level of gas exchange was determined at chamber temperature of 25°C . At 40 minutes after injection, the animals were again placed in the gas-exchange chamber, and the level of gas exchange was again determined. Amytal resistance in the cold-adapted albino mice, in which respiration and phosphorylation disturbances were noted formerly, was much higher than in the controls. This fact confirms the uncoupling of respiration and phosphorylation following cold adaption and permits the use of amytal for control of this phenomenon when the uncoupling mechanism is connected with the increased amytal resistance. It was also shown that amytal resistance in the respiration of cold-adapted animals correlates with their increased resistance to the narcotic action of amytal. This result confirms the data of other authors on the connection between the hypnotic effect of barbiturates and their ability to inhibit respiration. Since a high respiration level is maintained at the expense of nonphosphorylation reactions, it is supposed that in definite physiological conditions there may exist a more direct relationship between the respiration level and the functional cerebral activity.

M. N. Lomonosov Order of Lenin and Order of the Red Banner State University
U.S.S.R.

See also: 1069, 1071, 1112, 1117, 1125, 1126, 1138, 1153, 1157, 1162, 1278, 1279, 1281, 1287, 1291, 1292, 1293, 1297, 1298, 1300, 1304, 1306, 1307, 1311, 1312, 1315, 1316, 1321, 1323, 1326

BIOCHEMISTRY

- 1579 Smith, Jerry A., Waddell, William J., & Butler, Thomas C. **Demethylation of n-methyl derivatives of barbituric acid, hydantoin, and 2,4-oxazolidinedione by rat liver microsomes.** *Life Sciences*, 2(7):486-492, 1963.

This study concerns the N-demethylation by rat-liver microsomes of several N-methyl derivatives of barbituric acid, hydantoin, and 2,4-oxazolidinedione. The livers were removed from decapitated male Carworth Farms DFN rats weighing about 250 g, and a microsome preparation was made. This preparation (2.5 ml) was added to 2.5 ml of a solution containing 100 μ mole nicotinamide, 1.4 μ mole NADP, 10 μ mole glucose-6-phosphate, 68 μ mole semicarbazide, and 2 mg of one of the nine substrates tested. With the exception of 3-methylcholanthrene, the drugs tested for enzyme-inducing activity were given daily for 3 days. The rats were killed on the fourth day. The daily doses were: phenobarbital, 20 mg; nikethamide, 50 mg; diphenhydramine, 2 mg; and meprobamate, 5 mg. A single dose of 3-methylcholanthrene was given 1 day before the rats were killed. Demethylation was accompanied by formaldehyde production. There were large differences among the substrates in their rates of demethylation. Livers of rats pretreated with phenobarbital or nikethamide had higher demethylating activity toward all the substrates than did livers of untreated rats, but the degree of augmentation of activity was quite different for the different substrates.

University of North Carolina
Chapel Hill, North Carolina

- 1580 Smith, S. E. **Uptake of 5-hydroxy[^{14} C]tryptophan by rat and dog brain slices.** *British Journal of Pharmacology and Chemotherapy*, 20(1):178-189, 1963.

The uptake mechanism of the brain and the action on it of various compounds of pharmacological interest were studied. In particular, the effects of methyldopa and phenylalanine, two inhibitors of l-amino acid

decarboxylase, were examined. Slices of the brains from female black and white hooded rats (50 to 89 days old) and from male greyhound dogs were incubated at 37° or 0° C in Krebs-Ringer solution containing radioactive (C^{14}) and nonradioactive 5HTP; extracts were subjected to ascending chromatography. The experiments performed were: effect of incubation time and temperature and substrate concentration on 5HTP- C^{14} uptake, radiochromatography and chemical partition of brain extracts, action of methyldopa and other amino acids on uptake of 5HTP- C^{14} and 5HTP decarboxylase, the action of three potent inhibitors of decarboxylase (m-hydroxybenzylamine, 4-bromo-3-hydroxybenzylamine, and N-o-hydroxybenzyl-N-methylhydrazine), analysis of inhibition by methyldopa (5×10^{-3} M) and phenylalanine (10^{-3} M), effect of prior treatment with reserpine (5 mg/kg i.p., 22 hours before death) or iproniazid (100 mg/kg i.p., 24 and 2 hours before death), inulin uptake, and uptake by different parts of dog brain. Rat-brain slices take up and concentrate 5HTP- C^{14} when incubated at 37° C in vitro. Uptake is inhibited by methyldopa and phenylalanine in a competitive manner. Only a small proportion of 5HTP- C^{14} is decarboxylated. This observation and the lack of correlation between the effects of various inhibitors on uptake and on decarboxylase suggest that the two processes are not linked. In the cold, some passive diffusion of the amino acid occurs. In the dog brain, uptake varies from one part of the brain to another, being greatest in the caudate nucleus. The implications of the uptake mechanism in the treatment of animals, or of patients, with large doses of amino acids are discussed.

St. Thomas's Hospital Medical School
London, England

- 1581 Sharman, D. F. **A fluorometric method for the estimation of 4-hydroxy-3-methoxyphenylacetic acid (homovanillic acid) and its identification in brain tissue.** *British Journal of Pharmacology and Chemotherapy*, 20(1):204-213, 1963.

This report is concerned with the development of a specific fluorometric method for determining homovanillic acid (4-hydroxy-3-

methoxyphenylacetic acid) and with the identification of this compound as a normal constituent of brain tissue. The reaction was also applied to other organic acids and to some compounds structurally related to homovanillic acid. Tissues of dogs, cats, rabbits, cows, and sheep were extracted. The reagents for the reaction were ferric chloride and sodium hydroxide. Two-dimensional chromatograms were developed using four solvent systems. The characterization of the fluorescence from homovanillic acid, the effect of light on the reaction, the time of reaction with ferric chloride, the effect of reagent concentration, the stability of the fluorescence, the final procedure for the estimation of homovanillic acid, the specificity of the method, the use of the reaction as a localizing test on chromatograms, and the identification of homovanillic acid in brain tissue are discussed and/or illustrated. The fluorescence reaction for the estimation of homovanillic acid appears to be a general reaction for a number of compounds related to 4-hydroxy-3-methoxyphenylethane. This lack of absolute specificity requires that these substances be separated from the tissue extracts beforehand. The nature of the fluorescent substance has not yet been determined. The experiments show that there is a normally high concentration of homovanillic acid in the caudate nucleus of several species, higher than in the corpus striatum, which indicates the importance of COMT and MAO in the metabolism of the endogenous dopamine in the brain.

Agricultural Research Council Institute of Animal Physiology
Cambridge, England

1582 Krnjević, K., Laverty, R., & Sharman, D. F. **Iontophoretic release of adrenaline, noradrenaline, and 5-hydroxytryptamine from micropipettes.** British Journal of Pharmacology and Chemotherapy, 20(3):491-496, 1963.

The amounts of adrenaline, noradrenaline, and 5HT released by iontophoresis from micropipettes have been estimated. Twelve multi-barrelled micropipettes were used, four containing 0.13 M 5HT creatinine sulfate, four containing 0.75 M adrenaline acid tartrate, and four containing 1.7 M acidified noradrenaline. The amount of iontophoretic release of drug was plotted against the electrical charge after making correction for any spontaneous leakage of drug. In most experiments, the amount released was linearly related to the total electrical charge, but the

transport numbers for different pipettes, filled with samples of the same solution of adrenaline or of noradrenaline, varied substantially. Two pipettes containing noradrenaline failed to release any appreciable amounts of the drug. The transport number of 5HT was relatively constant. The most significant results of the present experiments were the substantial variations in the effective transport number determined when a similar current flowed through samples of the same solution of a drug in different micropipettes. Evidently one cannot assume that iontophoresis is a strictly quantitative method of application of drugs when comparing different compounds, and it is clearly essential to make observations with several pipettes before drawing any general conclusions about the effectiveness of any drug.

Agricultural Research Council Institute of Animal Physiology
Cambridge, England

1583 Barlow, R. B., Scott, K. A., & Stephenson, R. P. **An attempt to study the effects of chemical structure on the affinity and efficacy of compounds related to acetylcholine.** British Journal of Pharmacology and Chemotherapy, 20(3):509-522, 1963.

Two groups of compounds are studied to determine the effects of chemical structure on the affinity and efficacy of compounds related to acetylcholine. Compounds of the first set differ from those of the second set in that they contain a diphenylmethyl group (or a benziloyl group) in place of a methyl group. The former compounds are antagonists of acetylcholine, whereas most of the latter act like acetylcholine. The affinity constants of the former compounds for the acetylcholine receptors of the guinea-pig ileum and the equipotent molar ratios relative to acetylcholine for the latter compounds have been measured. The variation of the affinity constant with the constitution of the onium group in the antagonists (the diphenylmethyl compounds) was sufficiently consistent from one series to another for it to seem likely that corresponding changes in affinity with the constitution of the onium group would occur in the agonists. From the relative activity of the agonists and with this knowledge of relative affinity, it was possible to assess the effects of their structure on efficacy. Substitution of one methyl in the onium group by an ethyl group in these compounds increased affinity but decreased efficacy. The replacement of a second methyl by a second ethyl group had little effect on

affinity but decreased efficacy still further. The replacement of the ester link in acetylcholine by a 4-ether oxygen atom (as in the diphenylmethoxypropyl and methoxypropyl compounds) did not appreciably reduce affinity but markedly reduced efficacy, whereas the replacement of the ester link by a 3-ether oxygen atom (as in the diphenylethoxyethyl and ethoxyethyl compounds) markedly reduced affinity but did not reduce efficacy. The diphenylbutyrylmethyl compounds had low affinity and the butyrylmethyl compounds had low efficacy. It was concluded that the action of acetylcholine at the postganglionic parasympathetic receptors in the guinea-pig ileum depends upon the presence of the 4-carbonyl group (and presumably the onium group) for affinity and on the 3-ether oxygen atom and the trimethylammonium group for efficacy.

University of Edinburgh Medical School
Edinburgh, Scotland

- 1584 Laszlo, I. Removal of interfering nucleotides from brain extracts containing substance P. Effect of drugs on brain concentrations of substance P. British Journal of Pharmacology and Chemotherapy, 21(1):113-126, 1963.

Because the nucleotides adenosine 5'-monophosphate and adenosine 5'-triphosphate interfere with the estimation of substance P in brain extracts, several methods for their removal from mouse-brain extracts (using 22- to 30-g male albino mice) have been studied using adsorption chromatography, paper chromatography, extraction, precipitation, and enzymic methods. Of these, the enzymic method using adenylic acid deaminase was the only one found suitable. This enzyme deaminates adenosine monophosphate to 5'-inosinic acid, an inactive compound that does not influence the estimations of substance P; the adenosine triphosphatase content of the enzyme extract inactivates ATP. Adenosine monophosphate deaminase activity was estimated by a single colorimetric method that measures the ammonia liberated from adenosine monophosphate. Substance P in mouse-brain extracts was estimated after treatment of the animals with various drugs and after the enzymic removal of the interfering nucleotides. The drugs tested were: LSD-25, reserpine, morphine sulfate, chloroform and ether, chlorpromazine, barbitone sodium, insulin, phenytoin sodium, leptazol, and benzhexol hydrochloride. The drugs had no effect on the substance P content of mouse brain. The effects of these drugs on

contractions of the guinea-pig ileum induced by substance P and on the estimations of substance P are discussed.

University of Edinburgh
Edinburgh, Scotland

- 1585 Brownlee, G. & Johnson, E. S. The site of the 5-hydroxytryptamine receptor on the intramural nervous plexus of the guinea-pig isolated ileum. British Journal of Pharmacology and Chemotherapy, 21(2):306-322, 1963.

This paper describes experiments that localize the site of action of 5HT at the intramural parasympathetic ganglion cell of the guinea-pig ileum. Dose-response measurements (five to six doses) were made on the guinea-pig isolated ileum (from adult female guinea pigs) with six agonists: acetylcholine, 5HT, nicotine, dimethylphenylpiperazinium iodide, choline phenyl ether, and histamine. The dose effects were repeated in the presence of 12 antagonists (hyoscine HBr, procaine HCl, 5HT creatinine SO₄, hexamethonium HBr, pentolinium H tartrate, mecamlamine HCl, pempidine tartrate, nicotine H tartrate, dimethylphenylpiperazinium iodide, phenoxybenzamine chloride, LSD-25 tartrate, and 2-bromolysergic acid diethylamide tartrate) and one anticholinesterase (N,N'-diisopropylphosphorodiamidic fluoride). The specific actions of each compound are discussed and elucidated graphically.

King's College
Strand, London, W.C.2, England

- 1586 Greene, Nicholas M. & Spencer, Edward L., Jr. Diethyl ether and lactate dehydrogenase activity in vitro. Journal of Anesthesiology, 24(1):23-28, 1963.

This study was designed to determine the effect of one anesthetic, diethyl ether, on lactate dehydrogenase (LDH) activity in vitro. A simple in vitro system was used to eliminate the possible effects of ether on other enzyme systems. An excess of ether was used to accentuate its action. The methods used were based on the principle that when LDH, pyruvic acid, and reduced diphosphopyridine nucleotide (DPNH) are added together, the rate of disappearance of DPNH, as measured spectrophotometrically, measures the reaction velocity. Diluted Worthington beef-heart LDH was added to cuvettes containing 0.1 ml of 95.5% pure sodium pyruvate (0.01 or 0.001 M), 0.06 ml DPNH (0.159mg),

and potassium dihydrophosphate buffer. Distilled water (1.7 ml) was added to control cuvettes and diethyl ether (1.7 ml or 3,350 mg/100 ml) was added to the remainder. Controls were read before and after the ether cuvettes were analyzed. These two control readings showed that LDH activity tends to decline with time. The number of micromoles of DPMH consumed per minute was lower in the ether-containing cuvettes, however, than in either control cuvettes. Although this inhibition by ether is statistically significant, it is of little or no biochemical significance.

Yale University School of Medicine
New Haven, Connecticut

587 Wagner, J. W. & de Groot, J. **Multi-purpose cannula for acute and chronic intracerebral chemical and electrophysiological studies.** *Electroencephalography and Clinical Neurophysiology*, 15(1):125-126, 1963.

This communication describes a double cannula that can be used to study the effects of the intracerebral injection of minute quantities of chemical compounds. In addition, the device may be used for preinjection and postinjection electrical recording (monopolar or bipolar), electrical stimulation, or definitive lesion production. The basic components of the assembly are an adaptor with tubing inserted and flanged, an inner cannula, a paired outer cannula, and a baseplate. A diagram is given of these components. Illustrations are also given of the following: (1) the implanted outer cannula, with stereotaxic holder removed; and (2) the testing situation, with a rat connected, via delivery tubing, to the microinjector assembly. The device may be used for the deposition of compounds in solution or in crystalline form. It also makes possible a means for studying permanent destruction, as a sequel to transient (chemical) ablation, or for elucidating neural pathways by degeneration techniques.

University of California
Los Angeles, California

588 Brazier, Mary A. B. **Role of the limbic system in maintenance of consciousness.** *Anesthesia and Analgesia*, 42(5):748-751, 1963.

In this discussion of anesthetics and the conscious state, it is proposed that the three functions necessary to the conscious

state—(1) the transmission of the sense-labeled impulses bearing the message from the periphery to the brain; (2) awareness that the message has arrived; and (3) the storage of and ability to retrieve the message—are served, respectively, by the classical sensory systems, the nonspecific afferent system, and the phylogenetically old limbic system. Evidence that the third function is served by the limbic system, particularly by the hippocampus, comes from clinical neurophysiology, pathology, and animal experimentation. Recordings were made simultaneously from all three systems of the brain in the same animal (cat), unanesthetized and anesthetized (phenobarbital i.p.), while a controlled external stimulus was being applied. These recordings are included in the report.

University of California Medical Center
Los Angeles, California

1589 Brand, Leonard, Mark, Lester C., Snell, M. McM., Vrindten, P., & Dayton, Peter G. **Physiologic disposition of methohexital in man.** *Journal of Anesthesiology*, 24(3):331-336, 1963.

This paper attempts to evaluate some physicochemical and pharmacologic factors that influence the course of clinical anesthesia with methohexital in man. The chemical assay method described by Brodie and associates was modified for determining methohexital in plasma. Four human subjects received methohexital i.v. in 1% solution in doses of 1.2 to 1.8 g over a period of 1 hour. Plasma samples for determination of drug levels and rate of transformation were drawn at intervals over a 5-1/2-hour period. Samples of omental fat and plasma were obtained at intervals after a dose of 1.5 to 2.4 g methohexital was administered i.v. for 30 to 60 minutes to six patients undergoing operation, to determine the localization in tissues. In vitro studies were made to determine the partition coefficient, pK_a , and degree of plasma binding of methohexital. Changes in the electrical activity of the brain after i.v. injection of the drug were studied in man and dogs by an EEG. The rate of biotransformation and the extent of ionization of this anesthetic are in the same range as, but somewhat higher than, those for thiopental. In binding to plasma proteins, it is identical with thiopental. Its lipid solubility is high enough to permit rapid passage across the blood-brain barrier, but its accumulation in fat is less extensive than that of thiopental or methitural.

Columbia University
New York, New York

- 1590 Sullivan, James F., Lankford, Hal G., Swartz, Milton J., & Farrell, Charles. **Magnesium metabolism in alcoholism.** *American Journal of Clinical Nutrition*, 13:297-303, 1963.

Urinary magnesium excretion and serum magnesium levels were determined in 50 chronic alcoholics and 9 patients with Laennec's cirrhosis. The incidence of hypomagnesemia, its correlation with neurologic findings, and in particular, the efficiency of renal conservation of magnesium were evaluated. Low serum magnesium levels were present in 66% of the alcoholics and in 100% of those with delirium tremens, psychosis, coma, or severe neuropathy. Of the cirrhotic patients, four of nine had low serum magnesium levels without associated neurologic abnormalities. A significant and marked inability of the kidney to conserve magnesium, although the serum magnesium level was low, was demonstrated in some alcoholic and cirrhotic patients. The mechanism of this continued diuresis of magnesium is unknown. Abnormal excretion of zinc was found in 5 of 13 alcoholic patients and in 3 of 8 cirrhotic patients. There was no evidence suggesting correlation of magnesium and zinc excretion. In a limited number of patients, the magnesium excretion appeared to be independent of lactic acid excretion.

Creighton University School of Medicine
Omaha, Nebraska

- 1591 Golikov, S. N. & Pechenkin, V. A. A study of the penetration of certain cholinolytic drugs through the blood-brain barrier by perfusing the cerebral ventricles. *Bulletin of Experimental Biology and Medicine*, 56(11):1249-1251, 1963.

In this investigation, tests were made of the ability of three cholinolytics to pass through the blood-brain barrier: one quaternary--lachesine, and two tertiary--atropine and benactyzine. Twenty-seven cats were injected through the carotid artery in a dose of 4 mg/kg with the cholinolytic drugs. There were no toxic effects. Isolated rats' ileum was used to test the perfusion fluid, collected from the suboccipital space, for cholinolytic activity. The mean concentration in the perfusion was 9 μ g ($\pm$ 0.35) of benactyzine and 4.6 μ g ($\pm$ 0.26) of atropine; lachesine did not penetrate through the blood-brain barrier at all. These results indicate that differences in passage through the blood-brain barrier

exist not only between the tertiary and quaternary cholinolytics, but also between individual tertiary cholinolytics.

Institute of Toxicology, Ministry of Health of the U.S.S.R.
Leningrad, U.S.S.R.

- 1592 Bhagat, B. & Shideman, F. E. Mechanism of the positive inotropic responses to bretylium and guanethidine. *British Journal of Pharmacology and Chemotherapy*, 20(1):56-62, 1963.

A direct examination of the site and mechanism of the cardiac stimulation by bretylium and guanethidine was made by using isolated, atropinized, rat atria from male albino rats of the Holtzman strain, weighing 225 to 250 g. The rat atria exhibited positive inotropic responses to bretylium (5.0 μ g/ml), guanethidine (2.5 μ g/ml), and tyramine (0.25 μ g/ml). These compounds failed to elicit responses in atria from rats pretreated with 1.5 mg/kg i.p. of reserpine. Addition of dichloroisoprenaline (2.0 μ g/ml) to the bath also prevented these responses. The positive inotropic effects of these compounds on atria from reserpinized rats were restored by incubation of the tissue with noradrenaline (2 μ g/ml) for 30 minutes. The results indicate that these drugs liberate catecholamines from the heart. Atria from rats treated with reserpine did not show any increased sensitivity to noradrenaline, but were less responsive to tyramine. Guanethidine depleted the levels of endogenous catecholamines in the rat heart and impaired the uptake of adrenaline, whereas bretylium had no effect on either. The depletion of catecholamines from the rat heart by guanethidine was prevented by treatment of animals with 10 mg/kg of 1-phenyl-2-hydrazinopropane or with bretylium (5 mg/kg).

University of Minnesota
Minneapolis, Minnesota

- 1593 Bogdanski, D. F., Bonomi, L., & Brodie, B. B. Occurrence of serotonin and catecholamines in brain and peripheral organs of various vertebrate classes. *Life Sciences*, 2(1):80-84, 1963.

The distribution, storage, and release of 5HT and the catecholamines epinephrine and norepinephrine (NE) have been studied to determine whether these processes in the nerve endings of lower vertebrates are basically similar to those of mammals. The

levels of 5HT, NE, and epinephrine and the ratio of 5HT to catecholamine were determined in the tissues of the following species: the brain, heart, stomach, and small intestine of the rabbit and rat; the brain of the pigeon and chicken; and the brain, heart, stomach, and small intestine of a lizard, two species of frogs and toads, three species of salamander, and two species of fish. The occurrence of 5HT and the catecholamines in the brain of all vertebrate classes suggests that these antagonistic systems have had a long phylogenetic history. Amphibia differ from other vertebrates in that their brain contains epinephrine instead of NE. Since the brain of fish contains NE, modern amphibia probably descended from ancestral stock whose brain catecholamine was NE, but why epinephrine became the main catecholamine in amphibian brain is not understood. Also, NE is the main amine in the peripheral organs of salamanders but not of birds and toads. In a number of lower vertebrates, levels of brain amines are much higher than in mammals, partly because of the development of the cortex in mammals, which contains hardly any amines. The brain of birds, reptiles, and amphibia contains much more 5HT than catecholamines; in amphibia the ratio of 5HT to NE is as high as 10:1.

National Heart Institute
Bethesda, Maryland

- 1594 Wende, C. Vande & Spoerlein, M. T. Oxidation of dopamine to melanin by an enzyme of rat brain. *Life Sciences*, 2(6):386-392, 1963.

Because there is considerable speculation concerning the potential role of dopamine as a member of the extrapyramidal system and its possible relationship to the biochemistry of Parkinson's disease, it was of interest to examine whether dopamine undergoes oxidation to melanin in the brain. Homogenates of the brain (minus the cerebellum) of male albino rats, weighing 350 to 450 g, were prepared. The assay mixture contained 0.8 ml brain preparation, 1.0 ml dopamine (3 mg/ml) in 0.1 ml sodium phosphate buffer, and 0.2 ml buffer. (For comparison, equivalent amounts of DOPA and epinephrine were used instead of dopamine in separate determinations. Oxidation was assayed colorimetrically by measuring the optical density of the melanin formed during the reaction. Under the conditions of these experiments, dopamine was oxidized to a black pigment that was characterized as melanin by solubility tests and by its absorption proper-

ties. A figure shows the progression of melanin production with time of incubation. No melanin was formed when DOPA or epinephrine was used as the substrate. Because of the ready oxidation of dopamine to melanin, the possibility exists that dopamine is the substrate for the formation of melanin in the substantia nigra, since it is more concentrated in this region than DOPA or the other catecholamines. This would be in agreement with the concept that dopamine is related to the biochemistry of Parkinson's disease. Other considerations of this reaction are discussed.

Rutgers, The State University
Newark 4, New Jersey

- 1595 Hamberger, B., Norberg, K. -A., & Sjöqvist, F. Cellular localization of monoamines in sympathetic ganglia of the cat. A preliminary report. *Life Sciences*, 2(9):659-661, 1963.

Ganglion cells of the cat with a high variation in fluorescence intensity were demonstrated, both in normal and preganglionically denervated ganglia (2-weeks' survival). Axons showed faint fluorescence; neurons lacked this fluorescence completely; and clusters of cells adjacent to the capsule in the prevertebral ganglia showed very strong fluorescence in the yellow-green. Reserpine treatment (5 mg/kg, 24 hours) prevented the development of specific fluorescence in the terminals. It may be concluded that sympathetic cell bodies contain noradrenaline that transmits the fluorescence. No fluorescence was found in parasympathetic ciliary ganglion cells. A comparison of the occurrence of cholinergic and adrenergic neurons was made, using the "sweat secretory" ganglia. Cell bodies exhibiting high acetylcholinesterase activity lacked specific fluorescence for monoamines. In ganglia practically lacking cholinergic neurons, some degree of specific fluorescence was observed.

Karolinska Institute
Stockholm, Sweden

- 1596 Weber, L. J. & Horita, A. Oxidation of 4- and 5-hydroxyindole derivatives by mammalian cytochrome oxidase. *Life Sciences*, 2(1):44-49, 1963.

The cytochrome oxidase system was tested as the pathway for the oxidation of 4- and 5-hydroxyindoles. Cytochrome oxidase (type 1) was prepared from pig heart. Substrates

used included: psilocin; 4-hydroxytryptamine (4HT); 4-hydroxy-N-diethyltryptamine (CZ-74); 5HT; 5HTP; 5-hydroxy-N-dimethyltryptamine (bufotenin); and tryptamine. All of these indole substrates were oxidized by the cytochrome oxidase system, but the 4-hydroxyindoles were consistently better substrates. The order of oxidation for the 4-hydroxyindoles is as follows: 4HT > psilocin > CZ-74. Of the 5-hydroxyindoles, 5HT has the greatest activity, and bufotenin and 5HTP have less. Cytochrome oxidase must be considered in metabolic studies of these indoles in vitro.

University of Washington
School of Medicine
Seattle, Washington

- 1597 Roukema, P. A., Kafoe, W. F., Ernsting, M. J. E., de Roos, A. M., Funcke, A. B. H., & Nauta, W. Th. **Indoloquinolizine metabolites as a complicating factor in establishing brain serotonin levels.** *Life Sciences*, 2(11):799-803, 1963.

In the course of investigations into the properties of the sedative compound cis-1,2,3,4,6,7,12,12b-octahydro-2-methylindolo[2,3-a]quinolizine (BS 7128), it was found that brain and spleen tissue of rats who had received 50 mg/kg BS 7128 p.o. or 10 mg/kg BS 7128 i.v. showed about 100% increase in the fluorescence at 540m in 3 N HCl. This increase was, at first, attributed to increased serotonin levels. Reserpine-induced serotonin depletion, however, was not reversed when tranlycypromine or iproniazid was given to the BS 7128-treated rats. The possibility that the increased fluorescence was caused by a metabolite of BS 7128 was then tested. From these tests, it was found that a metabolite of BS 7128 that is hydroxylated in the 9 position was causing the increased fluorescence. The metabolite is a member of a new class of compounds that show spectrofluorometric resemblance to serotonin. Other substances of related structure may give rise to similar phenomena and, if not carefully checked, to unwarranted conclusions.

Vrije Universiteit
Valerinsplein, Amsterdam, Netherlands

- 1598 Askew, Beryl M. **A simple screening procedure for imipramine-like antidepressant agents.** *Life Sciences*, 2(10):725-730, 1963.

A screening procedure is described for differentiating potential antidepressant agents with imipramine-like activity from

tranquilizing agents in mice, in which the criterion of activity is a statistically significant antagonism of reserpine-induced hypothermia. Female albino Schofield mice (21 to 25 g in weight) were given 2 mg/kg reserpine s.c. and then housed for 17 hours at about 20°C. The rectal temperature of these reserpine-treated mice fell to 21°C to 24°C after 17 hours. Groups of 8 to 10 mice were then injected i.p. with the various test drugs or water, and the rectal temperature was measured hourly up to 6 hours after the injection. Imipramine, desmethylinipramine, and amitriptyline, in doses as low as 2 mg/kg, 1 mg/kg, and 2 mg/kg, respectively, produced a significant rise in rectal temperature compared to controls. The MAO inhibitors (iproniazid, phenelzine, and nialamide) also produced a rise in temperature. Although not entirely specific for antidepressants, evidence suggests that potential antidepressants would give a positive response in this test. The most satisfactory results were obtained when the environmental temperature at which the experiment was carried out was maintained as near as possible to 20°C. As the temperature rose above this level, there was an increasing tendency for the control mice to show some degree of spontaneous recovery over the time course of the test, thus making interpretation of the results more difficult.

John Wyeth & Brother
Havant, England

- 1599 Beck, F. & Lloyd, J. B. **The preparation and teratogenic properties of pure trypan blue and its common contaminants.** *Journal of Embryology and Experimental Morphology*, 11(1):175-184, 1963.

Studies were made to determine which of the fractions present in commercial trypan blue is responsible for its teratogenic action. A paper chromatographic method was devised to isolate and separate the blue and purple fractions. The red fraction was prepared by solvent extraction. Methods are described for each separation. Teratogenic properties of the fractions were tested in Wistar rats from an inbred laboratory strain propagated from brother-sister mating. The fractions were injected s.c. at 8.5 days of pregnancy in doses of 50 mg/kg. Control animals received 5 ml/kg normal saline. Another series of rats received 50 mg/kg control trypan blue. The rats were killed at 20.5 days pregnancy, resorption sites were counted, and fetal damage tabulated. Control trypan blue produced abnormalities in 71.1% of all potential off-

spring. The blue fraction produced abnormalities in 84% of potential offspring. The blue fraction appears to be the teratogenic component in trypan blue. The impurities were not active teratogens, and did not modify qualitatively the teratogenic activity of the blue fraction.

University College of South Wales and Monmouthshire
Cardiff, Wales, Great Britain

1600 Johnson, D. E., Millar, J. D., & Burchfield, H. P. **A new extraction technique for isolating chlorpromazine metabolites from urine.** Life Sciences, 2(12):959-962, 1963.

By adapting a method used previously for the isolation of the glucuronides of 17-ketosteroids, a procedure was developed by which chlorpromazine metabolites can be isolated from urine in two well-defined fractions by successive extraction with dichloromethane (DCM) and tetrahydrofuran (THF). The DCM fraction contains relatively nonpolar compounds, such as the suffoxide and dealkylation products of chlorpromazine. The THF fraction contains highly polar compounds and conjugates. Both fractions are amenable to further analysis by gas-liquid chromatography or thin-layer chromatography. The procedure was evaluated on urine specimens from 15 female and 10 male patients (19 to 83 years of age) receiving from 100 to 1,050 mg chlorpromazine daily for at least 5 months. The technique appears to work well with extraction of urine samples from patients receiving thioridazine and compazine; the test may be generally useful for isolating phenothiazine metabolites.

Southwest Research Institute
San Antonio, Texas

1601 Halpern, B. N., Neveu, T., & Spector, S. **On the nature of the chemical mediators involved in anaphylactic reactions in mice.** British Journal of Pharmacology and Chemotherapy, 20(3):389-398, 1963.

Various types of antagonists were used to investigate the nature of the mediators, histamine and 5HT, released in anaphylactic reactions in mice. The effects of the antagonists mepyramine, promethazine, chlorpromazine, and LSD were compared on the capillary permeability changes of the skin produced by histamine, by 5HT, and by passive cutaneous anaphylaxis. Promethazine,

mepyramine, and chlorpromazine can inhibit, in decreasing order of activity, the effect of histamine, but LSD is inactive. The LSD and chlorpromazine are equally potent in inhibitors of the action of 5HT on the peripheral vascular bed, but mepyramine is inactive. Promethazine had intermediate activity. Passive cutaneous anaphylaxis is strongly inhibited by chlorpromazine and by promethazine. Mepyramine and LSD, each injected alone, exert a weak effect on the anaphylactic reaction. Passive cutaneous anaphylaxis is almost completely abolished by the simultaneous injection of mepyramine and LSD. It is suggested that the anaphylactic reaction in mice is the result of simultaneous release of both mediators, histamine and 5HT, each of them strengthening the effect of the other.

Hôpital Broussais
Paris, France

1602 Alatyrev, V. I. & Zefirov, L. N. **The effect of disturbance of acetylcholine metabolism on cathode threshold parabiosis curves and on the functional stability of the nerve trunk.** Bulletin of Experimental Biology and Medicine, 55(3):239-242, 1963.

The effects of impaired acetylcholine synthesis were studied on the development of parabiosis in nerves. Nerve-muscle preparations from the frog (*Rana ridibunda*) were used in the experiments. Acetylcholine synthesis was impaired by preliminary (6 to 10 days before experimentation) removal of the frog's pancreas or by treating the nerve preparation with the cholinesterase inhibitor 2-methylnaphthoquinone. With both methods of impaired synthesis, there was an accelerated development of parabiosis when the nerve was stimulated by a direct-current cathode. When acetylcholine synthesis is disturbed, the functional resistance of the nerve, in relation to the action of factors producing alteration, is lowered. Resistance in the course of alterations is also lowered, as a result of which the curves of threshold cathodic parabiosis show a more rapid, deeper fall than curves derived from controls. The restorative processes within the nerve are also inhibited.

Kazan Medical Institute
Kazan, U.S.S.R.

- 1603 Sweeney, Daryl Dopamine: Its occurrence in molluscan ganglia. Science, 139(3539):1051, 1963.

Several lamellibranch and gastropod species were assayed for catecholamines. The three sets of ganglia of each lamellibranch were dissected free and pooled, and the entire circumesophageal ganglionic complex of the gastropods was removed. Fluorometric and paper chromatographic evidence derived from these samples indicates that dopamine is the only catecholamine definitely present. This demonstration that dopamine is the principal catecholamine in molluscan ganglia suggests that dopamine has a function independent of its role as the precursor to norepinephrine.

Harvard University
Cambridge, Massachusetts

- 1604 Perry, Thomas L. N-methylmetaneph-
rine: Excretion by juvenile psycho-
tics. Science, 139(3555):587-589, 1963.

As part of a study to determine possible roles of abnormal amine metabolism in mental illness, a preliminary survey was made of the amines present in the urine of 18 juvenile psychotics. The children were all outpatients and were not receiving tranquilizers. They were variously diagnosed as having childhood schizophrenia, infantile autism, or juvenile psychosis. The amine N-methylmetanephine was detected in the urine of 3 of the 18 children. This amine was not found in 20 normal children or 15 mentally defective children. Monoamine oxidase blockade increased the excretion of this amine, but produced no alteration in the behavior of the children. Administration of a strictly plant-free diet did not decrease the amine excretion. It is not clear whether this tertiary amine plays a part in causing some forms of psychosis or is merely a secondary result of mental dysfunction. Urinary excretion of bufotenin and of 3,4-dimethoxyphenylethylamine, each of which has been reported elevated in some adult schizophrenics, was not unusual in these children.

California Institute of Technology
Pasadena, California

- 1605 Brandt, Richard, Olsen, Marvin J., &
Cheronis, Nicholas D. Apparent con-
centration quenching of morphine fluores-
cence. Science, 139(3539):1063-1064, 1963.

Fundamental fluorescence equations were examined. Deviations from the theoretical were observed by varying the light path

length to determine effects on "apparent" fluorescence. The "effective" optical light path can, in theory, be lengthened by increasing the cuvette width. It was found that the decrease in emission of morphine solutions with the increase in concentration was caused by absorption effects that prevented excitation of the whole system.

Brooklyn College
Brooklyn, New York

- 1606 Burn, J. H., Rand, M. J., & Wien, R.
Adrenergic mechanism in the nictitating
membrane. British Journal of Pharmacol-
ogy and Chemotherapy, 20(1):83-94, 1963.

Experiments were conducted with perfused cat's head, in which many cholinergic nerve fibers were present in the nerve supply to the nictitating membrane. Contractions of the right nictitating membrane were recorded by attaching the membrane to an isotonic level with a frontal writing point. Shielded electrodes were placed on the post ganglionic nerves beyond the superior cervical ganglion. Submaximal postganglionic nerve stimulation with eserine sulfate perfusion produced an immediate increase of 80% in contractions. Atropine sulfate returned the contractions to original size. In cats under chloralose anesthesia, submaximal nerve stimulation after injection of atropine reduced nictitating membrane response, whereafter eserine produced a 2.5-fold increase in response. Injection of adrenaline or noradrenaline, followed by atropine, produced a decline of 10% in contraction height that, after injection of eserine, gradually returned to its original level, without increasing the contraction produced by injection of noradrenaline. Nictitating membrane contractions produced by hyoscine remained unchanged at higher frequencies of maximal stimuli, but were reduced at lower frequencies. The increase in contraction height produced by eserine or neostigmine was inversely proportional to the frequency of stimuli.

Biological Research Laboratories, May &
Baker
Dagenham, England

- 1607 Andén, Nils-Erik, Roos, Björn-Erik, &
Werdinius, Bengt. On the occurrence
of homovanillic acid in brain and cerebro-
spinal fluid and its determination by a
fluorometric method. Life Sciences, 2(7):
448-458, 1963.

A study was made of 3-methoxy-4-hydroxy-phenylacetic acid (homovanillic acid, HVA), formed by the metabolic attack by MAO and

catechol-O-methyl transferase (COMT) on dopamine (DA), in regard to the turnover of DA in the brain. The apparent HVA extracted by a method developed for this purpose was determined by paper chromatography. Human cerebrospinal fluid, obtained by lumbar puncture, also was extracted and determined chromatographically. In four experiments on untreated rabbits, the concentration of HVA in the corpus striatum was found to be 1.72, 2.04, 2.38, and 2.15 $\mu\text{g/g}$. The concentration of DA in the caudate nucleus was approximately 7.5 $\mu\text{g/g}$, and in the whole corpus striatum was 2.5 $\mu\text{g/g}$. No significant amounts of HVA were found in the cerebellum. The cerebral hemispheres, less the corpus striatum, contained approximately 0.2 $\mu\text{g/g}$, and the brain stem contained about 0.9 $\mu\text{g/g}$. The distribution of HVA in the brain was found to be the same as that of DA. The HVA was found in a concentration of 0.10 $\mu\text{g/ml}$, normally, in human lumbar cerebrospinal fluid. The HVA level in corpus striatum is increased about sevenfold after administration of l-DOPA, and is greatly decreased after administration of nialamide or (2-(3,4-dihydroxyphenyl)-hexanoylamide, a COMT inhibitor.

University of Göteborg
Göteborg, Sweden

- 1608 Kopin, I. J. & Bridgers, W. **Differences in d- and l-norepinephrine- H^3 .** Life Sciences, 2(5):356-362, 1963.

The relative binding rates and metabolism of d- and l-norepinephrine- H^3 were studied through examination of labeled myocardial and splenic catecholamines. Rats were administered s.c. 1.5 ml of either d,l-norepinephrine- C^{14} with d,l-norepinephrine- H^3 , or l-norepinephrine- C^{14} with d,l-norepinephrine- H^3 . The animals were killed at either 1 hour or 24 hours later, and the H^3/C^{14} ratio in the tissue catecholamines in heart and spleen was determined. One hour after administration of the labeled catecholamines, the H^3/C^{14} ratios of norepinephrine in the heart and spleen were found to be similar in animals given mixtures containing l- or d,l-norepinephrine- C^{14} . This indicates that both d- and l-norepinephrine- H^3 are taken up and bound by the heart and spleen at approximately the same rate. After 24 hours, the tissues of animals receiving l-norepinephrine- C^{14} and d,l-norepinephrine- H^3 showed more C^{14} relative to H^3 than that of animals receiving d,l-norepinephrine- C^{14} and d,l-norepinephrine- H^3 . The decrease in the H^3/C^{14} ratio of tissue norepinephrine in animals receiving l-norepinephrine- C^{14} and d,l-norepinephrine- H^3 was not due to an isotope

effect, and must have been due to a more rapid decrease in d-norepinephrine- H^3 than in l-norepinephrine- H^3 .

National Institute of Mental Health
Bethesda, Maryland

- 1609 Pscheidt, G. R. & Himwich, H. E. **Chicken brain amines, with special reference to cerebellar norepinephrine.** Life Sciences, 2(7):524-526, 1963.

In the course of a survey of normal distribution of norepinephrine and serotonin in brain regions of different species, the chicken cerebellum was found to contain relatively high amounts of norepinephrine. White Leghorn chickens were decapitated; the brains were rapidly removed and frozen; and the serotonin and norepinephrine content of the hemispheres, midbrain, pons-medulla and cerebellum was analyzed. Low levels of serotonin and appreciable amounts of norepinephrine were found in the chicken cerebellum. In an additional experiment, the norepinephrine content of the cerebellum was determined in five different species (in $\mu\text{g/g}$): chicken 0.62, dog 0.18, rabbit 0.09, rat 0.08, and guinea pig 0.26. Very little norepinephrine has been reported in the cerebellum of humans (0.02 $\mu\text{g/g}$) and fish (0.01 $\mu\text{g/g}$). Higher serotonin levels were found in the hemispheres than in the midbrain of the chicken. This finding may be related to the fact that the avian telencephalon is comprised mainly of subcortical structures with small amounts of neocortex, a structure known to exhibit low levels of serotonin and norepinephrine in mammals.

Galesburg State Research Hospital
Galesburg, Illinois

- 1610 Szara, Stephen. **Enzymatic formation of a phenolic metabolite from lysergic acid diethylamide by rat liver microsomes.** Life Sciences, 2(9):662-670, 1963.

To contribute to settling the problem of the metabolic pathways of LSD, the enzymatic hydroxylation of LSD by rat- and guinea-pig-liver microsomes was reexamined. Male guinea pigs and male albino rats were decapitated; their livers were removed immediately, chilled, homogenized, and centrifuged, and the enzyme microsomal sediments and the clear supernatant fractions were incubated with LSD. The LSD remaining in the reaction mixture was estimated by spectrophotometry and fluorimetry. Although both rat- and guinea-pig-liver enzymes metabolized LSD, as meas-

red by the substrate disappearance technique, the acetic acid extract showed considerably greater activity for the rat enzyme. The rat liver extract incubated with LSD contained a fluorescent product with slightly different fluorescent peak than that of LSD itself, although the activation peaks were identical. The guinea-pig enzyme failed to produce such a metabolite. Chromatographic results indicate that the new metabolite is not substituted at the 2-position, but has a phenolic HO-group on the benzene ring. It is highly probable that the hydroxy group of the new metabolite is in the 13-position of the lysergic acid ring.

Saint Elizabeth's Hospital
Washington D.C.

- 1611 Mehrotra, K. N. & Dauterman, W. C.
Specificity of rat brain acetylcholinesterase for N-alkyl analogues of acetylcholine. *Journal of Neurochemistry*, 10(2): 119-123, 1963

In a study of the substrate specificity of cholinesterases with regard to acyl choline substrates, the N-alkyl group specificity of the enzyme from rat brain was investigated. Seventeen analogues of acetylcholine were synthesized and tested. Rats were killed by a blow on the neck; the brains were removed, homogenized in ice cold water, and lyophilized; and the powder was used for assay. The greatest acetylcholinesterase activity occurred with the dimethyl and diethyl alkyl esters. In general, activity was inversely proportional to length of alkyl chain within any given dialkyl series. Trimethyl and triethyl analogues had greatest activity. The triethyl ester showed greater activity than the diethyl methyl ester, and at its optimal substrate concentration had 97% the activity of acetylcholine. Maximal activity for the di-n-propyl series was 22% the activity of acetylcholine, and for di-n-butyl series was 11% of the latter. No excess substrate inhibition was found for either the propylene or butylene analogue of acetylcholine. This result indicates a certain degree of specificity for the ethylene group.

Cornell University
Ithaca, New York

- 1612 Dauterman, W. C. & Mehrotra, K. N.
N-alkyl group specificity of choline acetylase from rat brain. *Journal of Neurochemistry*, 10(2):113-117, 1963.

In connection with studies of the occurrence and distribution of choline acetylase, the N-alkyl group specificity of this enzyme from

rat brain was studied with various analogues of choline. Seventeen choline analogues were synthesized and tested. Rats were killed by a blow on the neck, and the brains were immediately removed and ground in dry acetone in a cold mortar. The acetyl esters formed during incubation were determined by the hydroxylamine—ferric chloride method. The enzyme showed activity toward only 4 of the 17 analogues tested. All compounds with which the enzyme reacted were dimethyl derivatives suggesting that the enzyme is specific for the methyl groups of the nitrogen of the choline molecule. The kinetic constants of the enzyme in relation to choline increased for the longer chain derivatives, possibly because they offer steric hindrance and do not allow the substrate to reach the active site of the enzyme. Also, the enzyme was found to be specific with respect to alcohol chain length and could not acetylate the long chain derivatives of choline. The rates of acetylation reactions indicate that the enzyme has greatest affinity for choline, which is probably the normal substrate for the enzyme.

Cornell University
Ithaca, New York

- 1613 Peterson, N. A. & Chaikoff, I. L.
Uptake of intravenous-injected [4-C^{14}] cortisol by adult rat brain. *Journal of Neurochemistry*, 10(1):17-23, 1963.

Following i.v. injection of (4-C^{14})cortisol and (4-C^{14})cholesterol, 60 Long—Evans rats (180 to 220 grams) were killed at various intervals of up to 90 minutes by exsanguination from the vena cava. Either whole brain or 1 or 2 ml of plasma was digested with 0.5 M KOH, and the radioactivity was counted. Immediately after injection of 4-C^{14} cortisol, about 0.09% of the C^{14} appeared in the whole brain; the remainder then disappeared as a linear function of time. A typical first-order decay curve was obtained for disappearance of radioactivity from the plasma, with a half-life of 28 minutes. The amount of C^{14} incorporated into the brain was influenced by a prior injection of unlabeled cortisol. Each of 6 rats was given a single injection of (4-C^{14})cholesterol i.v. Cholesterol entered the brain most rapidly in the first few minutes after injection, and the rate then decreased with time. Eight hours after injection, 0.11% of the radioactive label was recovered in the brain. Comparison of the brain and plasma curves shows that after the initial rise following a single injection, labeled steroid is removed more rapidly from plasma than from brain. The results imply that as the con-

centration of plasma cortisol is elevated by repeated injections, steroid accumulates in the brain even without a net rise in plasma level.

University of California
Berkeley, California

- 1614 Johnson, E. S. Origin of the acetylcholine released spontaneously from the guinea-pig isolated ileum. *British Journal of Pharmacology and Chemotherapy*, 21(3):555-568, 1963.

In a study of the endogenous release of acetylcholine and inquiry into its origin, an investigation was made of the spontaneous output of acetylcholine by guinea-pig ileum. Longitudinal isotonic contractions of 3-cm segments from the middle and terminal ileum of adult guinea pigs were recorded in response to histamine, 5HT, and nicotine in a Krebs solution bath. The guinea-pig ileum was pretreated by incubation in Krebs solution containing the anticholinesterase mipafox (10 μ g/ml). Cocaine hydrochloride (5 μ g/ml), procaine hydrochloride (10 μ g/ml), and cooling the ileum to 25° C inhibited spontaneous output of acetylcholine and muscular response, with the exception of the response to histamine. Calcium depletion (one-twentieth the usual level) modified the effects of all three agonists and inhibited acetylcholine output; replacement of calcium with an equal amount of strontium chloride eliminated all drug response, although one-third the normal acetylcholine output was recorded. A fourfold increase in magnesium content of the bath did not alter drug response but greatly reduced acetylcholine output. Hemicholinium-3 produced little modification of drug response but greatly inhibited spontaneous output of acetylcholine. It is concluded that the spontaneous output of acetylcholine originates in parasympathetic nerve endings of the intramural nerve plexuses.

King's College
Strand, London, England

- 1615 Carlini, E. A. & Green, J. P. Subcellular distribution of histamine, slow-reacting substance and 5-hydroxytryptamine in the brain of the rat. *British Journal of Pharmacology and Chemotherapy*, 20(2):264-277, 1963.

To determine whether or not histamine occurs in particulate material of the brain, the brains of three or four rats, killed by de-

capitation, were pooled, homogenized in sucrose, and centrifuged at 1,200, 10,300, 100,000 and 90,000 g, yielding fractions F-1 to R-6. These fractions were extracted with dilute HCl, boiling dilute HCl, acetone, boiling dilute HCl plus acetone, n-butanol, and two types of ion-exchange chromatography. Histamine was determined by fluorimetry and bioassay, and succinic dehydrogenase by spectrophotometry. The slow-reacting substance and 5HT were determined by bioassay. All fractions of whole-brain extract produced a slow contraction of guinea-pig ileum that was not blocked by boiling or by the antihistamine, mepyramine. The greatest effect was produced by the F-4 fraction, obtained by density-gradient centrifugation of large particulate material. The acid-acetone extract, whether boiled or unboiled, also inhibited contractions due to histamine. Duration of inhibition was proportional to the concentration of the extract. Equated to histamine effect, the concentration of this active substance in the brain would be 253 mg/g. Histamine in the extracts was separated by chromatography. Most of the histamine was found in small particulate material, whereas the slow-reacting substance was found in particulate material of greater density, and 5HT was present in both small and large particles. Succinic dehydrogenase was not associated with any of the three substances. It is possible to suggest that the R-4 fraction contained pinched-off nerve endings.

Yale University School of Medicine
New Haven, Connecticut

- 1616 Sjoerdsma, A. & von Studnitz, W. Dopamine- β -oxidase activity in man, using hydroxyamphetamine as substrate. *British Journal of Pharmacology and Chemotherapy*, 20(2):278-284, 1963.

A study was made, aimed at developing a method for assessing dopamine- β -oxidase activity in the intact human. Hydroxyamphetamine hydrobromide tablets or capsules were given to five hospital patients, who had no significant renal or hepatic disease, every 6 hours for from 2 to 5 days, in a daily dose of from 26 to 118 mg. All the patients had the regular hospital diet. One patient had undergone a second adrenalectomy 21 days before the test. Paper chromatography showed a great increase in excretion of a basic compound, identified as free and conjugated hydroxynorephedrine, the β -hydroxylated metabolite of hydroxyamphetamine. It was found that about half the total dosage of hydroxyamphetamine was excreted in each patient as unchanged drug (free plus con-

jugated). The highest percentage of hydroxylation occurred in totally adrenalectomized patients. The β -hydroxylation of hydroxy-amphetamine in vivo, which has not been described previously, may be demonstrated by the simple method used in this study.

National Heart Institute
Bethesda, Maryland

- 1617 Asatoor, A. M., London, D. R., Milne, M. D., & Simenhoff, M. L. **Excretion of pethidine and its derivatives.** British Journal of Pharmacology and Chemotherapy, 20(2):285-298, 1963.

The fate of meperidine was investigated in man during states of mild metabolic acidosis and alkalosis with urinary pH at the extremes of the physiological range. Meperidine HCl (100 mg) was given s.c. to patients without hepatic or renal disease, who required moderate analgesia. The drug and its metabolites were estimated by the methyl-orange method of Burns et al. (1955). Dinitrophenyl derivatives of normeperidine and norethoheptazine were determined by reversed-phase paper chromatography. Meperidine output is highest during the first 2 hours after injection, then it drops logarithmically, falling below the level of chemical detection after 36 hours. Excretion of the metabolite normeperidine rises to a maximum 4 to 8 hours after injection, then falls gradually and is negligible after 48 hours. It can, however, be detected chemically during the third and, occasionally, the fourth day. In highly acidic urine, the greater proportion of output in the first few hours is unchanged drug, which drops rapidly to a very low level 18 hours after injection, whereas in alkaline urine, unchanged drug accounts for less than 25% of the total output. In highly acid urine, the mean output of unchanged meperidine is 22% of the injected dose, and that of normeperidine is 34% of the dose. In alkaline urine the mean cumulative excretion of both meperidine and normeperidine amount to only 4% of the dose.

University of London
London, England

- 1618 Häkkinen, Hertta-Maija & Kulonen, E. **Comparison of various methods for the determination of γ -aminobutyric acid and other amino acids in rat brain with reference to ethanol intoxication.** Journal of Neurochemistry, 10(6):489-494, 1963.

The paper-electrophoretic, the paper-chromatographic, and the enzymatic methods for the determination of GABA and other amino

acids in rat brain were compared, in the hope of finding an adequate quantitative procedure suitable for serial samples. Using these methods, an attempt was made to confirm earlier results on ethanol-induced changes in brain amino acids and to check the effect of fasting on brain amino acids. Wistar rats, 200 to 250 g in weight, were fasted 24 hours and then were given 550 mg ethanol/100 g body weight. The rats were killed 2 hours later and the brains dissected. A control series of rats that were not fasted was employed. The paper-electrophoretic and paper-chromatographic methods were applied to the analysis of brain amino acids. The electrophoretic method gave values that were too high for aspartic and glutamic acids, and too low for glutamine. For the determination of GABA, the enzymic method was also employed. The partly purified *Pseudomonas Fluorescens* preparation used contained GABA- α -ketoglutaric acid transaminase and succinic semialdehyde dehydrogenase, but also impurities, which reoxidized the NADPH in the presence of brain extracts. In an aged enzyme preparation, these impurities were decreased, but they still remained a source of error. The effect of ethanol on brain amino acids of fasting rats, observed earlier by a chromatographic method, was confirmed also by the electrophoretic method and, in regard to GABA, by the enzymic method. In fed rats, the effect of ethanol on the amino acid concentrations in brain was absent.

Research Laboratories of the State Alcohol Monopoly
Helsinki, Finland

- 1619 Laverty, R., Michaelson, I. A., Sharman, D. F. & Whittaker, V. P. **The subcellular localization of dopamine and acetylcholine in the dog caudate nucleus.** British Journal of Pharmacology and Chemotherapy, 21(3):482-490, 1963.

The distribution of dopamine between the subcellular fractions from homogenates of dog caudate nucleus was compared with the distributions of acetylcholine, 5HT, and lactate dehydrogenase activity. The distributions of noradrenaline and 5HT between the subcellular fractions from homogenates of dog hypothalamus were also determined. In initial experiments, brain homogenates were separated into total particulate material and high-speed supernatant fluid. In other experiments, the homogenates were separated initially into three primary particulate fractions. Most of the dopamine, in contrast to acetylcholine, occurred in the soluble supernatant fraction.

The percentage distribution of dopamine in the three primary particulate fractions from caudate nuclei was similar to that found for 5HT, both being less sharply localized than acetylcholine. When sub-fractionation of the crude mitochondrial fraction was performed, dopamine was not as closely associated with any one sub-fraction as acetylcholine. Evidence is presented that suggests that dopamine occurs in a free and easily released form throughout cell cytoplasm.

Agricultural Research Council
Institute of Animal Physiology
Babraham, Cambridge, England

See also: 1069, 1115, 1117, 1162, 1163, 1164, 1166, 1168, 1172, 1173, 1175, 1177, 1182, 1201, 1208, 1211, 1215, 1227, 1231, 1243

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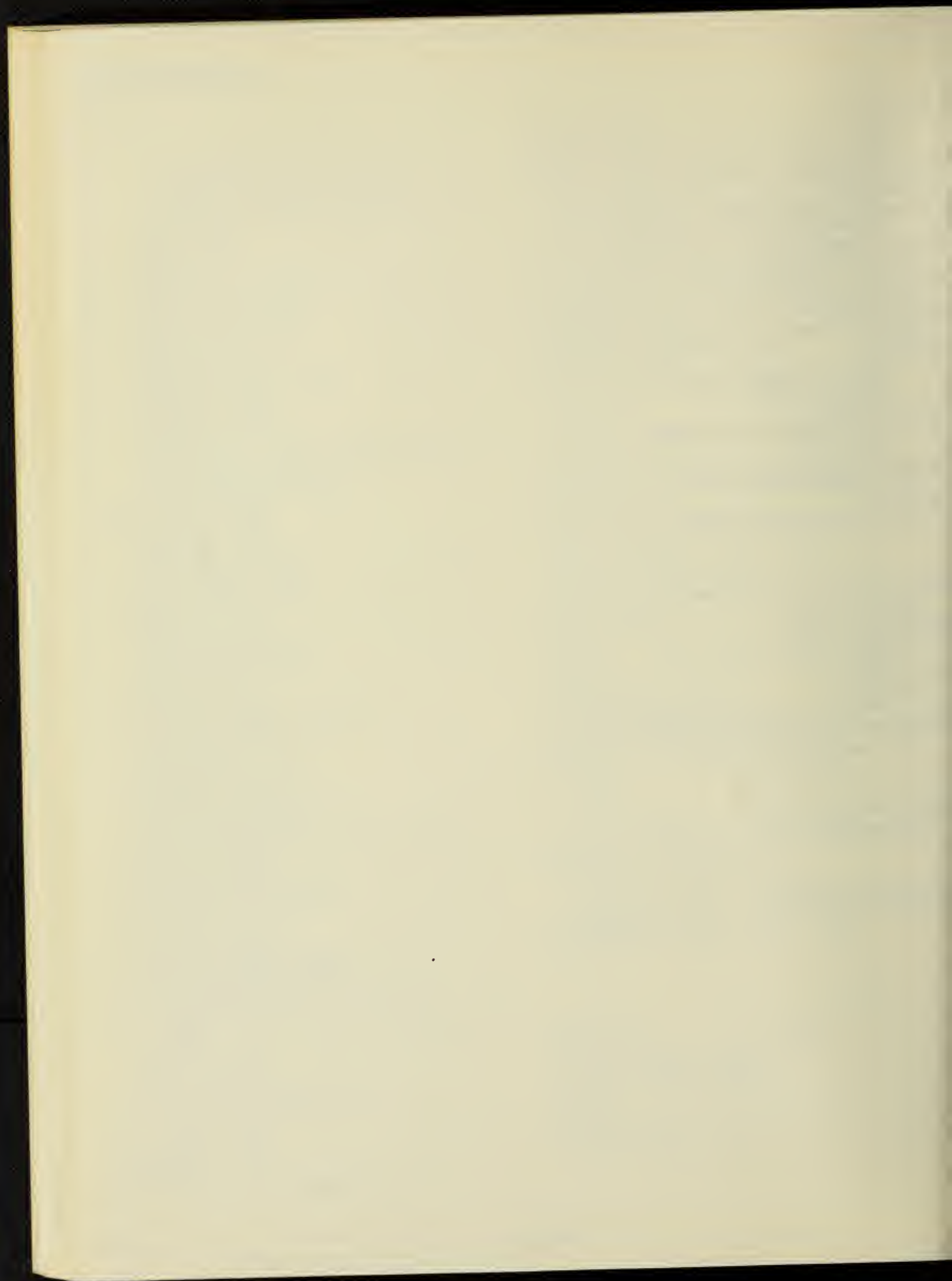
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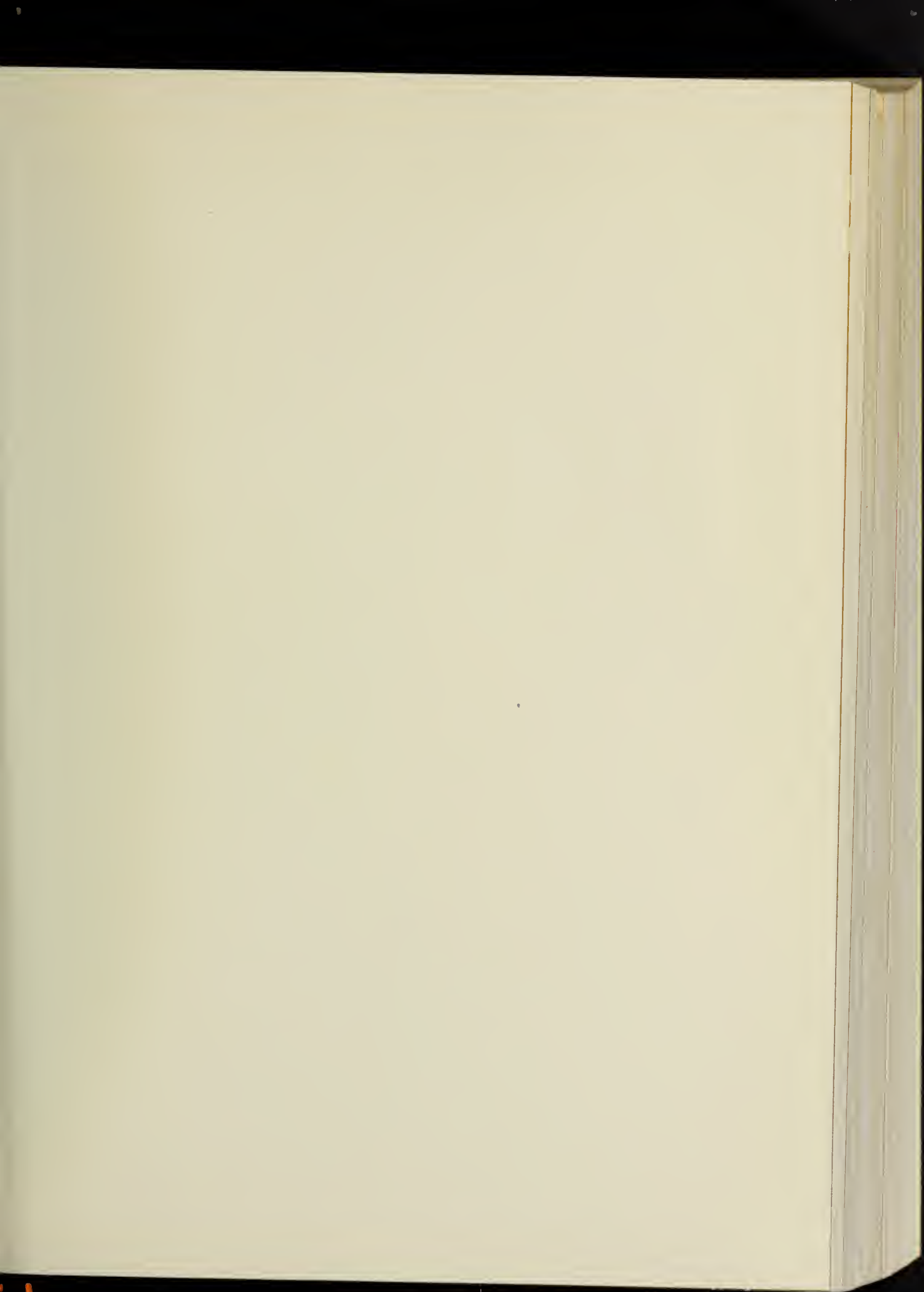
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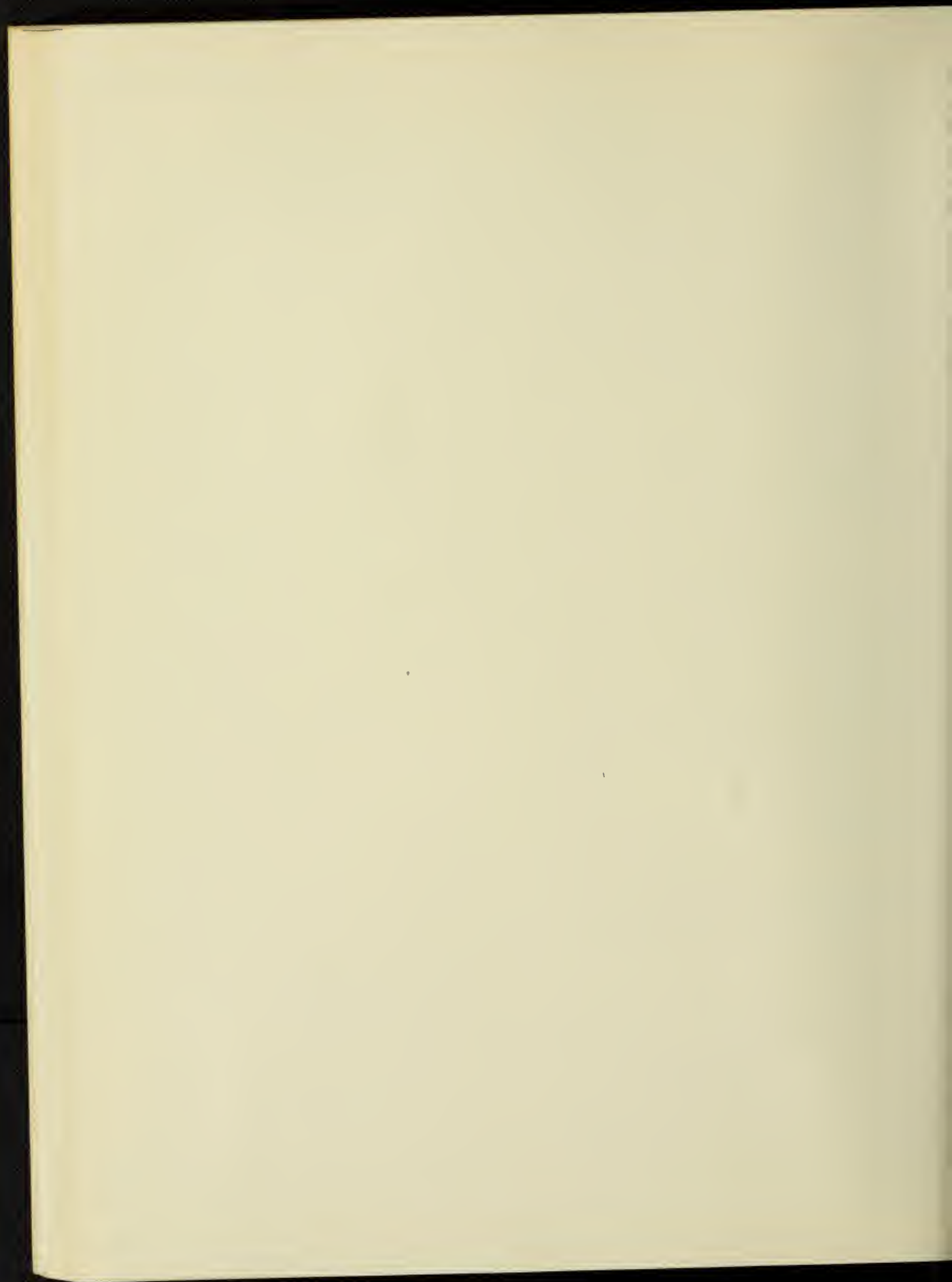
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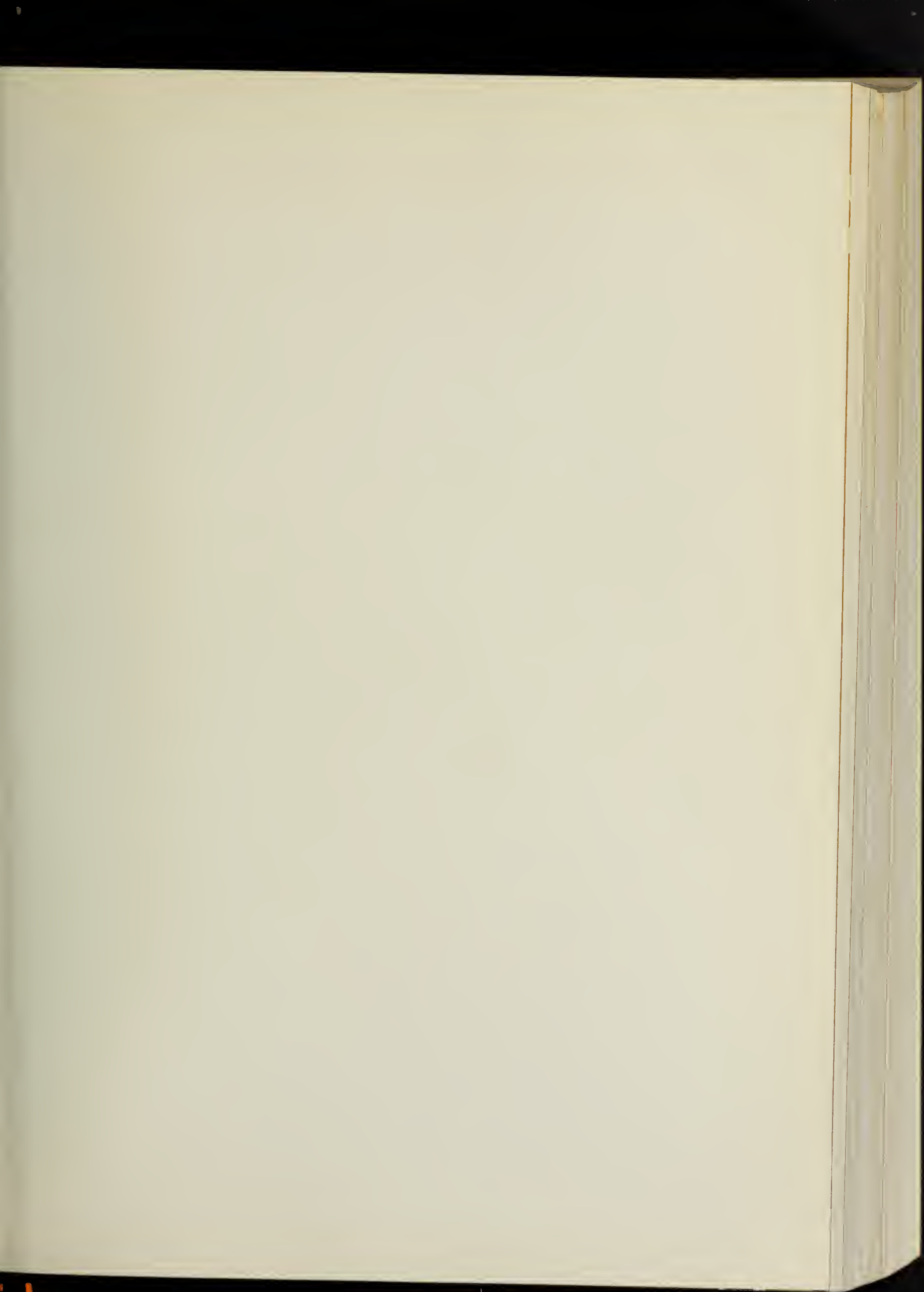
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NATIONAL CLEARINGHOUSE FOR MENTAL HEALTH INFORMATION

PSYCHOPHARMACOLOGY ABSTRACTS

Vol. 3 No. 8

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

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PSYCHOPHARMACOLOGY ABSTRACTS

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REVIEWS, SUMMARIES, BIBLIOGRAPHIES, GENERAL ARTICLES AND BOOKS

- 1620 **Today's Drugs. Drugs for obesity.** British Medical Journal, 2(5361): 853-855, 1963.

In a review of drugs used in treatment of obesity, the following are considered: anorectic drugs (all related to amphetamine), thyroid hormone, other hormones, diuretics, sedatives and tranquilizers, methylcellulose, and slimming foods. Pharmacology and side effects are indicated.

(No address)

- 1621 Brauner, F. & Pringuet, G. **Les traitements médicamenteux des enfants déficients mentaux. (Drug treatment of mentally defective children).** Revue de Neuropsychiatrie Infantile, 11:571-582, 1963.

A review is given of the observations of many authors on the use of psychopharmacological agents for the treatment of mentally deficient children, together with a list of the drugs that have been used for this purpose. Slightly and moderately deficient children are improved by neuroleptics and, to a lesser degree, by tranquilizers. The agitated, grossly deficient are refractory to drug therapy, and most authors report temporary or no improvement, even with the strongest neuroleptics. Apathetic, inhibited, autistic, and occasionally the unstable mentally deficient children may be improved by psychotonic amines and thymoanaleptics. The combination of psychoanaleptics with psycholeptic drugs reported by many authors appears promising. Reports indicate that psychopharmacological effects of drugs do not always coincide with their clinical effects: amphetamines with supposedly stimulant effect have produced stabilizing effects in agitated children. A similar reaction may be observed with certain MAO inhibitors in many cases of psychic instability. Because deficient children have only a negative factor in common, their incapacities, it is difficult to compose groups of comparable equivalents. Consequently there is little agreement as to doses and results of treatment. (30 references)

Paris, France

- 1622 **Barbiturate poisoning.** Lancet, 2(7322):1367-1368, 1963.

Acute barbiturate intoxication treatment should include measures to reduce absorption, to abate dangerous systemic effects, and to enhance the poison-removal rate. With long-acting barbiturates, there is a great risk of irreversible cerebral damage and severe respiratory infection. Short-acting barbiturates (cyclobarbitol, pentobarbitol, and secobarbitol) and ultrashort-acting compounds used as anesthetics (thiopental and hexobarbitol) are not likely to produce long-continued coma. The rate at which barbiturate is eliminated from the body is enhanced by polyuria and alkalinity of the urine. In the therapy of 57 patients, two solutions were used for infusion---a 50% urea solution in physiological saline (80 ml i.v. every hour for 4 hours) and an electrolyte solution (300 ml i.v.) containing sodium lactate, sodium chloride, potassium chloride, and glucose, designed to alkalinize the urine and to prevent electrolyte depletion from the osmotic diuresis produced by the urea. Only three of the 57 patients died. In a minority of cases, tracheostomy is necessary and, in patients with renal damage, hemodialysis is a very effective treatment.

(No address)

- 1623 **Antidepressants.** Journal of the American Medical Association, 183(11): 951-952, 1963.

The usefulness of amitriptyline HCl and isocarboxazid (an MAO-inhibitor) as antidepressant agents is reviewed. Amitriptyline HCl appears to be useful in the management of the depressed phases of anxiety and manic-depressive states and in the treatment of involutional melancholia. Isocarboxazid seems to be effective in the depressed phases of anxiety and manic-depressive states, as well as in certain involutional, obsessive, and disassociative reactions. Because of its atropine-like activity, amitriptyline is contraindicated in patients with glaucoma and in patients

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REVIEWS 1624-1627

in whom urinary retention is a possibility. Since large doses of isocarboxazid can potentiate the effects of certain drugs, care should be taken when the following agents are administered concomitantly: psychotropic agents, alcohol, ether, barbiturates, meperidine, cocaine, procaine, phenylephrine and other sympathomimetic amines, opiates, antihypertensive agents, and insulin.

(No address)

- 1624 Domino, Edward F. **Chronic use of barbiturates and chloral hydrate.** Journal of the American Medical Association, 183(9):816, 1963.

Chronic use of barbiturates and chloral hydrate in large doses will produce a syndrome similar to chronic alcoholism. Doses larger than 400 mg/day for more than 30 days of short-acting compounds, such as pentobarbital, amobarbital, and secobarbital, are sufficient to produce marked physical dependence and withdrawal symptoms. A patient using 585 mg of these agents chronically is physically dependent. The continued use of these drugs may lead to brain damage and personality changes. It is suggested that patients taking barbiturates be given other sedatives, such as carbromal, glutethimide, meprobamate, or chlordiazepoxide, although they may also produce physical dependence.

Ann Arbor, Michigan

- 1625 **The use of the terms habituation and addiction.** Journal of the American Medical Association, 183(5):363, 1963.

Because the continued use of the terms "habituation" and "addiction" for non-narcotic drugs may lead to misinterpretation by legislators, law-enforcement officials, laymen, and physicians, the Council on Drugs has decided to replace these terms in its statements with descriptions of the characteristics reported, or considered likely, to occur. This change will be effective in "New and Nonofficial Drugs 1963." In the JAMA, the Council's column, "New Drugs and Developments in Therapeutics," will reflect this policy, and all monographs and digests of new drugs appearing in this column will conform to this policy.

No address)

- 1626 **New drugs and developments in therapeutics.** Journal of the American Medical Association, 183(5):362-363, 1963.

Because the attention of the Council on Drugs has been drawn to discrepancies that exist in the 1962 edition of "New and Non-official Drugs," an account of revisions made in the monographs on amphetamines is given, and the fact that no specific reference to the word "addiction" occurs in any monograph on amphetamines in NND 1962 nor in the 1961 or 1962 monographs on phenmetrazine is stressed. Although the characteristics of either habituation or addiction may occur with any drug capable of modifying behavior, the need for special control measures depends on the extent of the problem. In the United States at this time, compulsive abuse of the amphetamines and/or the barbiturates is such a small problem that additional measures to control the abuse seem unnecessary. The Council on Drugs reaffirms the American Medical Association's position against the necessity or desirability of legislative control of these drugs similar to that now imposed on other drugs under the narcotics law.

(No address)

- 1627 Müller, Christian. **Über psychische Stimulation oder Dämpfung bei Sauerstoffmangel und ihre Beziehung zu psychopharmakologischen Problemen.** (Psychic stimulation or inhibition in oxygen deficiency and its relation to psychopharmacological problems.) Archiv für Psychiatrie und Nervenkrankheiten vereinigt mit Zeitschrift für die Gesamte Neurologie und Psychiatrie, 204:199-208, 1963.

The role of oxygen-deficiency studies in psychiatric experimentation is pointed out. Eight-hundred Swiss soldiers with low ven-trical pressure were surveyed, with emphasis on changes in psychic functions. Oxygen-deficiency experiments were then performed on a selected group of these men (aged 20 to 30 years). In the precollapse phase of a specific oxygen deficiency, three different reactions were manifested. The most common was a dullness of the leading short stimulation phase, while the rarest reaction was in the form of a progressive collapse. These varied reactions seemed to follow a changing personality pattern. Followup psychiatric examinations supported the finding. These oxygen-deficiency reactions were lessened by neuroleptic medication.

REVIEWS 1628-1630

Psychotropic drugs should be used in research in oxygen deficiencies and the relationship of psychic functions.

University Psychiatric Clinic
Lusanne, Switzerland

- 1628 Dittfurth, H. v. Aktuelle Strömungen in der Pharmakopsychiatrie. (Current trends in pharmacopsychiatry.) Therapeutische Umschau, 20:65-68, 1963.

Psychopharmacology is currently in a state of transition. A short review of past trends and a preview of the widening scope are presented. Experiences in neuroleptic therapy derived from clinical investigations suggest the use of drug combinations in therapy, such as the phenothiazine derivatives with a CNS stimulant. Chlorphencyclan is an example. In animal experiments, chlorphencyclan reduces the cataleptic activity of thiopropazate. Through these phenothiazine derivatives, inhibition of spontaneous motor activity and secondary reactions takes place. Such clinical findings with drug combinations should lead to correlation between pharmacological and clinical experiments. Since 1962, emphasis is being placed not on chemistry and pharmacology but on the overall psychiatric, psychopathological and clinical findings.

Lucerne, Switzerland

- 1629 Nakajima, H. & Gad, I. Die pharmakologische Therapie des schizophrenen Formenkreises. (Pharmacotherapy of diseases of the schizophrenic group.) Therapie der Gegenwart, 102:665-672, 1963.

The group of schizophrenic diseases is discussed on the basis of the classic categorization (hebephrenic, catatonic, and paranoid). Recently developed neuroleptic drugs are reviewed under the following groups: phenothiazine derivatives, Rauwolfia alkaloid derivatives, and the butyrophenones. Dosage of the neuroleptics is decreased until hypertonia occurs, at which time treatment is suspended. Interruption of chemotherapy enables observation of the patient's reactivity and evaluation of the therapeutic results obtained. Dosage may be stopped abruptly without lasting aftereffects. In refractory cases, EST may be applied. In chronic cases, neuroleptics, such as thioridazine, prothipendyl, methylpromazine, and centrophenoxine may be used with full effect and almost no side effects.

In schizophrenia with strong inhibitory effects, any neuroleptic with stimulant action may be used. Such neuroleptics may evoke a latent excitatory symptom, in which case, butyrophenones may be given. In schizophrenia with a state of excitation, neuroleptics with sedative effect was given. If they evoke a strong depressive clinical picture, it is advisable to give psychoanaleptics. Interruption of treatment is definitely of interest for observation of the status of the disease, and of indications for new treatment.

Unite de Recherches de
Neuro-Psycho-Pharmacologie
Paris, France

- 1630 Krüger, H. J. & Schwarz, H. Neue Aspekte der neuroleptischen Langzeit-Therapie in der psychiatrischen Ambulanz und Klinik. (New aspects of long term neuroleptic therapy of psychiatric outpatients and inpatients.) Medizinische Welt, 9:463-467, 1963.

Perazin (P 725) was tried on 337 male and 82 female inpatients (1 to 91 years old, mean age 31 to 40). The duration of clinical treatment ranged from 1 to 39 months, with an average of 6 months. The dosage ranged from 150 to 1,500 mg/day for the males (average 700 mg/day), and 150 to 1,000 mg/day for the females (average 450 mg/day). The therapeutic results were very good (VG), good (G), moderate (M), or unchanged (U), as follows: VG 42, G 206, M 98, U 73. For the 239 schizophrenics of this group, the results were: VG 28, G 134, M 43, U 34. Of these schizophrenics, 165 were released for outpatient posttreatment, in many cases at lowered dosage. Over a 3-year control period, 90 patients (54.5%) had acute relapse, with paranoid-hallucinatory psychoses accounting for 28 (17.0%), and acute exacerbation appearing in 49 defective schizophrenics (30.0%). Somatic side effects were relatively low in both clinical treatment and ambulatory posttreatment, including pronounced akinetic syndrome in 15, collapse-like reaction in 8, vomiting in 3, nausea in 4, intolerance in 4, moderate liver damage of unclear origin in 4 posttreatment cases, paradoxical reactions at high doses in several inpatients, and allergic reaction in 3 cases. There was no relapse in any case in which the patient and his family had good insight into the disease.

Palatinate Neurological Clinic
Landeck, Germany

631 Angst, J. *Psychopharmakologie und Familienforschung. (Psychopharmacology and family research.)* Schweizer Archiv für Neurologie, Neurochirurgie und Psychiatrie, 91:267-272, 1963.

Family research in schizophrenia has turned towards etiological and nosological questions in the last 20 years. No causal therapy of endogenous psychoses has been practiced; treatment has been more or less nonspecific and symptomatic. Clinical research, bodily restraint, and modern psychopharmacology activities have not placed emphasis on the individual illness nor on the diagnosis. Pharmacological techniques and pharmacological investigations in family research applications indicate that heredity is a partial factor in schizophrenia. An experiment with 60 blood-related psychotic patients using imipramine is reported. An endogenous familial depression with great similarities was found in the individual cases, which could not be traced solely to the presenting symptoms of the illness itself. Hereditary factors in the reactions to psychopharmaceutical drugs may be reflected in metabolism or in pathogenetic differences in the patient.

University of Burghalys
Burich, Switzerland

632 Chauchard, P. & Mazoué, H. *Effet comparé de divers excitants nerveux. (Comparative effect of various nerve excitants.)* Journal of Physiology, 55:229-240, 1963.

Effects of thymoanaleptics on the CNS are discussed, and several thymoanaleptics are compared. The drugs under consideration are: strychnine, maxiton, iproniazid, alamide, and imipramine.

École des Hautes Etudes, Sorbonne
Paris, France

633 Simon, Robert I. *Obesity as a depressive equivalent.* Journal of the American Medical Association, 183(3): 18-210, 1963.

The psychologic factors involved in obesity and the importance of taking these factors into account when treating the obese patient are reviewed. In connection with the Air Force Weight Control Program, 27 overweight men and 50 randomly selected non-obese personnel were questioned concerning depressive episodes within the past 2 years.

Of the 50 nonobese individuals, 13 had a history of significant depression, whereas only one of the 27 obese patients had had similar difficulty. The use of dextro-amphetamine sulfate as a weight-reducing agent is cited. The anorexigenic action of the drug may result from its euphoric effect, which relieves the patients' suppressed depressive tendency and the desire to overeat. This study indicates the statistically significant correlation between obesity and the relative absence of overt depression which should not be overlooked in planning and weight-reduction program.

USAF Dispensary, APO 76
San Francisco, California

1634 Hirshleifer, Irving & Kroger, William. *Benzodiazepines in the differentiation and treatment of anxieties.* Clinical Medicine, 70:1673-1678, 1963.

To study the effectiveness of diazepam in the treatment of depression and anxiety, the drug was administered to 106 patients in doses of 2 to 10 mg, b.i.d. from 1 week to more than 10 months. All of the patients (32 men and 74 women (19 to 78 years of age) showed overt signs of anxiety or depression or they had disorders frequently associated with these symptoms. Seventeen patients had angina pectoris and has previously responded well to chlordiazepoxide therapy. Results were as follows: 66 patients showed marked relief, 6 moderate, 3 fair, and 24 (including the 17 patients with angina pectoris) had no relief of symptoms. Whereas chlordiazepoxide increased appetite, diazepam did not exhibit this. Side effects of diazepam were minimal and included drowsiness, or nervousness, with headaches in three of the patients. It was concluded that chlordiazepoxide is broader in therapeutic spectrum than diazepam, but that diazepam is more effective (at one-fifth the dosage of chlordiazepoxide) than chlordiazepoxide in the psychiatric states of anxiety or depression.

Woodmere, New York

REVIEWS 1635-1641

- 1635 Usdin, E. & Amai, R. L. **Psychotropic and related compounds.** Psychopharmacology Service Center Bulletin, 2:17-93, 1963.

The chemical classifications, LD₅₀'s (mg/day), and trade names have been given for all drugs possessing psychotropic activity (tranquilizers, energisers, and hallucinogens and their related compounds).

Melpar, Inc.
Falls Church, Virginia

- 1636 **Today's drugs. Drugs for depression. Principles of treatment.** British Medical Journal, 1(5324):173-174, 1963.

A combination of treatments is generally used in the treatment of depression, since the biochemical and neurophysiological evidence is insufficient for reliable classification. Tranylcypromine and amphetamines potentiate the effects of adrenaline and other sympathomimetic amines. Combinations of these drugs may result in hypertensive crisis. The use of hydrazines such as, (phenelzine, nialamide, and isocarboxazid) carries an appreciable risk as well as limited benefit. Side effects caused by the hydrazines are jaundice, (sometimes fatal) agranulocytosis, and hypotension. The overall treatment of the depressed patient is not greatly advanced by drugs. Imipramine and amitriptyline, combined with ECT, substantially reduces the relapse rate. These drugs are less effective in severe depression than ECT; they are moderately toxic, causing dryness of mouth, parasympathetic blockade, and drowsiness, but the side effects diminish with repeated administration.

(No address)

- 1637 **Today's drugs. Drugs for depression.** British Medical Journal, 2(5354):799-802, 1963.

A panel discussion on drugs used in the treatment of depression is presented. Topics discussed include: (1) what is depression? (2) drug treatment; (3) approach to patients; (4) dangers of therapy; (5) has the treatment of depression improved? (6) when should a drug be released? (7) ethical questions; and (8) are drugs really worthwhile?

(No address)

- 1638 **Today's drugs. Hypnotics—2. Non-barbiturates.** British Medical Journal, 1(5323):107-108, 1963.

A brief review of available nonbarbiturate hypnotics is presented. Drugs discussed are chloral hydrate, the mono-ureides (carbromal), and new synthetic compounds (ethchlorvynol, ethinamate, glutethimide, methaqualone, methyprylone, methylpentynol, and propiomazine). It was concluded that all hypnotics may have side effects, may cause addiction, and may become a means of attempted suicide.

(No address)

- 1639 **Today's drugs. Drugs for Parkinsonism.** British Medical Journal, 1(5327):385-386, 1963.

The newer drugs for treatment of parkinsonism were discussed with respect to their effectiveness, side effects, and dosage. Some of the drugs mentioned are as follows: benzhexol, procyclidine, ethopropazine, phenglutarimide, orphenadrine, bengtropine, and chlorphenoxamine. The belladonna alkaloids were also mentioned as a possible treatment.

(No address)

- 1640 Benekens, J. **Drugs for parkinsonism.** British Medical Journal, 1(5331):678, 1963. (Letter).

Comment is made on a column (February 9 issue) concerning the use of orphenadrine in the treatment of akinesia and senile depressions. Comparison is made between the antihistamine and antiacetylcholine properties of orphenadrine and the properties of diphenhydramine.

Brussels, Belgium

- 1641 **Drugs and doctors.** British Medical Journal, 1(5334):835-836, 1963.

A general discussion of drug testing, designed to determine deleterious side effects, is presented. Cyclizine, meclizine, and imipramine are given as examples of drugs reported that may cause fetal

abnormality. Possible damage to the liver from halothane is also noted. For clinical testing of any drug, maximum cooperation between the medical profession and the drug industry is required.

(No address)

- 1642 Spencer, D. A. **Colour of tablets.** British Medical Journal, 1(5344):544, 1963. (Letter).

The antidepressant drug amitriptyline is available as a 25-mg tablet of a particular color. The hospital pharmacy issues a brand different from that generally supplied by druggists or prescribed by the family doctor. Complaints arise that patients are receiving the wrong drugs because of the different colors used for the same medicine. Many patients attach importance and faith to the color of a tablet and are not easily convinced that tablets of a different color are still the same drug.

t. James's Hospital
Leeds, England

- 1643 **Epilepsy and schizophrenia.** British Medical Journal, 1(5345):1557-1558, 1963.

Studies have shown that in the schizophrenias, as in epilepsy, there are symptomatic as well as idiopathic cases. In the idiopathic cases, heredity plays an important part, although virtually nothing is known of how heredity exerts its effects. In the symptomatic cases, the underlying causes seem to be cerebral disease or toxic agent such as amphetamine, dextroamphetamine, and/or alcohol, or, as in the schizophrenias of the aged, personality deviation, deafness, social isolation, and cerebral disease in varying combinations: heredity plays little or no part. Some authorities in the field conclude that in epilepsy accompanied by a schizophrenia-like psychosis, the schizophrenia is a symptomatic psychosis etiologically related to the epilepsy or the pathological causes underlying the epilepsy or both.

(No address)

- 1644 **To-day's drugs. Drugs in the treatment of Ménière's disease.** British Medical Journal, 1(5347):1719-1721, 1963.

Vertigo, nausea, vomiting, and anxiety accompany an attack of Meniere's disease. As treatment of the attack itself, i.m. injection of 12.5 mg prochlorperazine (1 ml of a 1.25% weight per volume solution) is given. Alternatively, 25 to 50 mg dimenhydrinate i.m., or 0.3 to 0.6 mg hyoscine i.m. can be tried. If practicable, all these can be given orally. To reduce the effects of the attack, the following drugs are commonly administered: phenobarbital and prochlorperazine; mepyramine and promethazine; dimenhydrinate and promethazine theoclate; and orphenadrine. To reduce the possibility of further attacks, nicotinic acid and buphenine are used. All the above drugs produce side effects, such as hypersensitivity, drowsiness, fatigue, confusion, euphoria, possible increase of tinnitus, nausea, and, in the case of the vasodilators, a tendency to postural hypotension. A table gives the specific side effects for specific drugs, together with dosages.

(No address)

- 1645 **Drugs and the human embryo.** Lancet, 1(7283):705-706, 1963.

Since about 1 child in 50 is born with a severe congenital malformation recognizable at birth, it is not easy to establish a satisfactory correlation between the taking of a drug by the mother and the birth of a deformed child. Before the impact of thalidomide, no deliberate search was made to discover teratogenic agents, such as salicylates, thyroxine, caffeine, and vitamin A. Misgivings have been expressed about the safety of meclizine, podophyllin, and tetracycline; laboratory experiments have recently indicated teratogenic effects after the administration of carbutamide, chlorpromazine, cyclizine, glybutiazole, imipramine, prochlorperazine, tolbutamide, triethylenemelaine, and triparanol. If the capability of a drug to produce malformations in laboratory animals is not to be an absolute bar to its use, some formula must be devised to express the danger to the embryo in relation to the therapeutic dose. Until more is known about the anatomy, physiology, and pharmacology of the embryo and the placenta, it is important to strike as satisfactory a balance as possible between letting a dangerous teratogen loose on the market and missing a drug of great therapeutic potential.

(No address)

REVIEWS 1646-1650

- 1646 Kessel, Neil, McCulloch, Wallace, & Simpson, Esme. **Psychiatric service in a centre for the treatment of poisoning.** British Medical Journal, 2(5363):985-988, 1963.

The operation of a psychiatric examination service to patients admitted to a center for the treatment of poisoning is described, and its advantages are outlined. An analysis of 490 nonfatal, deliberate self-poisoning cases (150 men and 286 women) admitted to a hospital is presented. Rates by sex, age, and marital status, and methods used, diagnosis, and the disposals are presented. The relationship of deliberate self-poisoning to attempted suicide is discussed.

Royal Infirmary of Edinburgh
Edinburgh, Scotland

- 1647 Braceland, Francis J. **Stimulants and tranquilizers—their use and abuse.** Bulletin of the New York Academy of Medicine, 39(10):649-665, 1963.

This paper, given as one of the Lectures to the Laity, 25th Annual Series, discusses the use of pharmacotherapy in psychiatry. The sequence of events that must be gone through before a drug can be used, as well as the overall view of the status of tranquilizers and stimulants in psychiatry is presented. The evaluation of a drug using the placebo response versus the therapeutic response; the addiction and habituation to sedatives, hypnotics, and tranquilizers; and their future as first-aid measures is also discussed.

The Institute of Living
Hartford, Connecticut

- 1648 **Persistence of barbiturates.** British Medical Journal, 2(5359):695-696, 1963.

The division of barbiturates into long-, medium-, short-, and ultrashort-acting by their rate of disappearance from the bloodstream is very useful in treating barbiturate poisoning, but it is less satisfactory in selecting the right barbiturate for a particular clinical purpose, because there is direct evidence that measurable effects persist for longer than the fall in concentration of the drug in the blood suggests. Loss of function, as compared with controls, has been demonstrated as much as 14 hours after 100 mg pentobarbital. Even

after thiopental, some prolonged effects have been observed electroencephalographically. Also, the actual duration of sleep is less dependent on the particular barbiturate than would be expected. The more rapidly metabolized barbiturates are less dangerous if an overdose is taken, so the advantage appears to be with quinalbarbital or pentobarbital. As the effect lasts longer than the drug, it is possible that once effective sedation is achieved sleep is easier not only for the rest of the night but on following nights.

(No address)

- 1649 Best, William R. **Drug-associated blood dyscrasias.** Journal of the American Medical Association, 185(4):286-290, 1963.

This article summarized information contained in the semi-annual résumés of the Registry on Blood Dyscrasia for 1962. Potassium perchlorate was added to the list of drugs believed to be responsible for the development of blood dyscrasias. The phenothiazines, chloramphenicol, and the sulfonamides continued to be reported to the Registry as being associated with blood-dyscrasia development. Physicians were urged to use therapeutic agents that are less hematotoxic when these agents would be as effective as the more toxic ones. Caution should be exercised with regard to new drugs or chemicals, particularly those used in the treatment of nervous and mental disorders.

University of Illinois College of Medicine
Chicago, Illinois

- 1650 **Drugs evaluated by the Council on Drugs. Summary of reports issued between June 30, 1962, and July 1, 1963.** Journal of the American Medical Association, 185(4):198-303, 1963.

Brief summaries of drugs evaluated by the Council on Drugs have been compiled, including information on uses, actions, and precautions of the following tranquilizers and antidepressants: amitriptyline HCl, buclizine HCl, chlordiazepoxide HCl, chlormezanone, emylcamate, hydroxyphenamate, isocarboxazid, mephenoqualone, oxyphenbutazone, phenyramidol HCl, piminodine ethanesulfonate, and propiomazine HCl.

(No address)

1651 Farnsworth, Dana L. Hallucinogenic agents. Journal of the American Medical Association, 185(11):878-880, 1963.

Many men and women, particularly college students, are taking the hallucinogens (stramonium, mescaline, LSD-25, psilocybin, marijuana, and morning glory seeds). These drugs exert powerful and often damaging effects on the human system. Clinical observations suggest that people who are attracted to the hallucinogenic drugs are often those most likely to be harmed by them; in taking these drugs, persons seek a method of changing reality and a solution to their inner conflicts. Patients and witnesses reported the following hazards of the drugs: strife, pornography, frustrating inability to communicate, an urge to do violence to children, uncontrollable sobbing, and other hallucinations that warrant the fraternity phrase, "hell experience." Clinical evidence demonstrates the power of these drugs to damage the individual psyche and even to cripple it for life; many have been hospitalized for long periods following the ingestion of small amounts of drugs. The ingestion or inhalation of any agent taken to alter a person's usual mental and emotional equilibrium must be considered a medical procedure. These drugs should be dispensed only when prescribed by licensed physicians with a warning as to the risks involved, and with a provision for their use for experimental purposes by responsible investigators under proper medical supervision.

Cambridge, Massachusetts

1652 Fox, Henry M. Psychiatric consultation in general medical clinics. An experiment in postgraduate education. Journal of the American Medical Association, 185(13):999-1003, 1963.

The psychiatric staff of a general hospital provided a consultant for each of a number of general medical clinics that replaced previous specialty clinics. In each of the medical clinics, consultation became more effective after the psychiatrist had established a working rapport with his colleagues over a period of from several weeks to several months. Regular meetings of the psychiatric consultants made it possible to compare their individual experiences and to gather typical examples of clinical situations in which this type of consultation was most effective. The use of tranquilizers and antidepressant medication presented psychopharmacological problems of considerable practical importance, as in the

case of a female, cyclothymic patient who seemed inexplicably apathetic until it was discovered that she had been taking fairly large doses of phenobarbital, chlorthalidone, and meprobamate. This study of the total clinical situation has given both internists and psychiatrists a more accurate perspective concerning the interrelationship of structural and function disturbance, particularly as this affects diagnosis, treatment, and the patient-physician relationship.

721 Huntington Avenue
Boston, Massachusetts

1653 Ayd, Frank J., Jr. Chlorpromazine: Ten years' experience. Journal of the American Medical Association, 184(1):51-54, 1963.

Over a 10-year period, chlorpromazine has been found to be a safe and effective drug that has played a fundamental role in the advancement of chemical treatment of mental illness. Although the drug is capable of eliciting a variety of pharmacologic and allergic responses, the risk of the latter is much less than was suggested by earlier reports. Clinicians have noted a steady decline in the incidence of dermatitis, jaundice (0.5%), and agranulocytosis (1 in 250,000 cases) caused by chlorpromazine. An investigation of chlorpromazine-induced hepatitis in 276 cases and agranulocytosis in 69 cases revealed that these reactions occurred more often in women than in men. Also discussed are the phenothiazines, which may cause extrapyramidal reactions, ranging from the various manifestations of akinesia to dyskinesia, akathisia, and parkinsonism. These neurologic reactions are often precipitated by fluphenazine hydrochloride, trifluoperazine hydrochloride, perphenazine, thiopropazate hydrochloride, and prochlorperazine, and less frequently by chlorpromazine, depending on the dosage used.

6231 York Road
Baltimore 12, Maryland

1654 New drugs and developments in therapeutics. Pargyline hydrochloride (Eutonyl). Journal of the American Medical Association, 184(11):887, 1963.

An evaluation of pargyline hydrochloride on the basis of available laboratory and clinical evidence has been presented. This MAO inhibitor seems to be an effective hypotensive agent. Postural hypotension

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evidenced by weakness, fainting, and dizziness can be prevented by reduction of the dosage. Adverse reactions with the use of pargyline include nausea, vomiting, constipation, insomnia, nervousness, sweating, dryness of the mouth, nightmares, headache, impotence, and delayed ejaculation. Pargyline should not be administered with drugs that affect the CNS nor should the drug be given to obese hypertensive patients. The usual dosage for adults (25 to 50 mg daily) should be reduced for geriatric patients. The initial dose of pargyline should not exceed 25 mg daily when given with other hypotensive agents.

(No address)

1655 Evaluation of chlorprotixene, (Taractan). Journal of the American Medical Association, 186(2):144-145, 1963.

Chlorprothixene, an antiemetic and a tranquilizer, is effective in the treatment of acute and chronic schizophrenic reactions and in those psychotic and severe neurotic conditions in which agitation, anxiety, and tension predominate. The drug is chemically and pharmacologically similar to the phenothiazines. The most frequent reactions are drowsiness, lethargy, xerostomia, orthostatic hypotension, tachycardia, dizziness, edema, constipation, anuria, convulsions, nervousness, syncope, insomnia, nasal congestion, and skin rash. These effects were readily reversible on reduced dosage or discontinuation of the drug. Chlorprothixene should be used with caution in patients with epilepsy or impaired kidney function, and is contraindicated in pregnant patients or patients with cardiac or cerebral vascular disorders. The drug is capable of potentiating the action of other CNS depressants and antihypertensive agents. Blood counts, periodic liver function tests, and thyroid function tests should be performed in patients receiving large doses of the drug. The dosage should be highly individualized. Recommended dosages are: 30 to 600 mg/day p.o. or 12.5 to 25 mg. i.m. for nausea; 75 to 200 mg may be given for the acutely agitated patient.

(No address)

1656 Phenylramidol hydrochloride (Analexin). Journal of the American Medical Association, 186(2):326, 1963.

The use of phenylramidol hydrochloride to relieve musculoskeletal pain and dysmenorrhea is reviewed. Side effects of the drug

are nausea, epigastric distress, drowsiness, pruritus, and skin rash. The drug should be administered p.o. 200 to 400 mg, t.i.d. or q.i.d.

(No address)

1657 Carphenazine maleate (Proketazine maleate). Journal of the American Medical Association, 186(10):944, 1963.

In this brief evaluation of carphenazine maleate, a member of the piperazine subgroup of phenothiazines, the following are described: action and use, side effects, precautions, pharmacology, route of administration, dosage, chemical name, preparations used, supplier, and year of introduction. Carphenazine maleate seems to possess a spectrum of activity similar to other members of the piperazine subgroup but of shorter duration. Useful in treating chronic or acute schizophrenia, its most frequent side effects have been somnolence and extrapyramidal symptoms, which occur particularly when large doses are used. It is recommended that patients taking the drug be closely observed for adverse reactions, since clinical experience is still inadequate.

(No address)

CLINICAL STUDIES

1658 **Evaluation of two tranquilizers acetophenazine maleate (Tindal maleate).** Journal of the American Medical Association, 186(10):943-944, 1963.

A brief evaluation of acetophenazine maleate, a member of the piperazine group of phenothiazine tranquilizers, describes the following: action and use, side effects, precautions, pharmacology, route of administration, dosage, chemical name, preparation, supplier, and year of introduction. Acetophenazine maleate seems to be effective in the treatment of chronic brain syndrome and severe neurotic conditions in which agitation, anxiety, and tension predominate. Side effects include drowsiness, lethargy, weakness, fatigue, and motor retardation; in many situations, use of the drug is not recommended.

No address)

1659 Sørensen, B. Florian. **Treatment of meprobamate withdrawal syndrome.** Journal of the American Medical Association, 186(13):1179, 1963. (Letter).

Symptoms arising after abrupt withdrawal of short-acting barbiturates or of meprobamate are best treated with phenobarbital 1 to 0.3 g t.i.d. for 2 or 3 days. After this period, phenobarbital is slowly withdrawn.

Copenhagen, Denmark

1660 McCormick, T. C., Jr. **Treatment of meprobamate withdrawal syndrome.** Journal of the American Medical Association, 186(13):1178-1179, 1963. (Letter).

Meprobamate must be classified with barbiturates, meperidine hydrochloride, and alcohol, in that abrupt withdrawal from excessive intake may produce a syndrome of toxic delirium, tremor, convulsions, and even death. The generally accepted treatment includes sedation (phenobarbital or chlorpromazine hydrochloride); use of anti-convulsants (such as diphenylhydantoin);

adequate fluid and nutritional intake, including vitamins; maintenance of electrolyte balance; and constant and close nursing attendance. Drug and nutritional therapy often require parenteral administration. Sedation and anticonvulsant therapy must be gradually decreased and withdrawn over a period of a week or more, as warranted in the individual case.

Austin, Texas

1661 Engelhardt, David M., Rosen, Bernard, Freedman, Norbert, Mann, David, & Margolis, Reuben. **Phenothiazines in prevention of psychiatric hospitalization.** Journal of the American Medical Association, 186(11):981-983, 1963.

To determine whether long-term phenothiazine treatment of outpatient schizophrenics prevents or delays hospitalization, 445 chronic schizophrenic outpatients (18 to 44 years old) admitted to a clinic between March 1958 and December 1961 were observed. Double-blind, noncrossover techniques were used in the random administration of chlorpromazine HCl, promazine HCl, or placebo. A preliminary study in 1960 on the first 173 patients admitted showed the following hospitalization rates for the three groups: (1) chlorpromazine, 4.8%; (2) placebo, 28.6%; and (3) promazine, 18.2%. By 1963, hospitalization rates of all 445 patients were evaluated as follows: (1) chlorpromazine, 19.0%; (2) placebo, 29.6%; and (3) promazine, 28.0%. A final tabulation was made in 1963 for the hospitalization rates of the clinic's original 173 patients: (1) chlorpromazine, 14.5%; (2) placebo, 32.1%; and (3) promazine, 27.3%. As chlorpromazine was effective in reducing the incidence of outpatient hospitalization primarily during early treatment, it was concluded that its effect represents a delay rather than a prevention of hospitalization.

Brooklyn, New York

CLINICAL STUDIES 1662-1666

1662 Moertel, Charles G., Reitemeier, Richard J., & Gage, Robert P. A controlled clinical evaluation of antiemetic drugs. *Journal of the American Medical Association*, 186(2):116-118, 1963.

A controlled, double-blind comparison of five antiemetics and placebo was made by administering the drugs (prochlorperazine, 5 mg; thiopropazate, 10 mg; pipamazine, 10 mg; cinnarizine, 10 mg; and trimethobenzamide, 200 mg) t.i.d. to 300 patients receiving the emetic fluorouracil. One hundred eighty patients were receiving a "first course" of fluorouracil therapy (in the hospital) and 120 were receiving a "second course" (outpatient basis). All antiemetics and placebo were administered p.o. 20 minutes before each meal, and each patient was seen daily for observation. Results showed that thiopropazate was most effective, followed in decreasing order of effectiveness by prochlorperazine, pipamazine, cinnarizine, trimethobenzamide, and, finally, placebo. The only side effect noted was oversedation, especially with the administration of thiopropazate and pipamazine.

Mayo Clinic
Rochester, Minnesota

1663 Hellier, F. F. A comparative trial of trimperazine and amylobarbitone in pruritus. *Lancet*, 1(7279):471-472, 1963. (Letter).

A series of patients with various skin conditions, including eczema and lichen planus was treated in a double-blind, controlled study for 2 weeks with similar tablets containing trimeprazine (10 mg t.i.d.) or amylobarbitone (50 mg t.i.d.). The patients were then reviewed and given a further supply of apparently similar tablets, although the tablets had been changed. At the end of the second 2-week period, the preferences of the patients were recorded. There was no significant difference in the preference for either drug. Drowsiness occurred in two patients, one taking each drug. Trimeprazine in the recommended dose has no advantage over amylobarbitone.

The General Infirmary
Leeds, England

1664 Armitage, P. Comparative trial of trimeprazine and amylobarbitone in pruritus. *Lancet*, 1(7281):661, 1963. (Letter).

From the comparative trial of trimeprazine and amylobarbitone in pruritus (see abstract 1663), no differences in treatment were found between trimeprazine and amylobarbitone. The method employed appears to have been applied incorrectly in this trial.

London School of Hygiene
and Tropical Medicine
London W.C.1, England

1665 Oldham, P. D. Trimeprazine and amylobarbitone in pruritus. *Lancet*, 1(7282):666-667, 1963. (Letter).

The author comments on the clinical trial and sequential method used in treating pruritus with trimeprazine and amylobarbitone (see abstracts 1663 and 1664). If the trial had been validly completed, the conclusion that trimeprazine has no advantage over amylobarbitone goes beyond what can legitimately be asserted. Criticism is made of the reliance that appears to have been placed on a technical statistical device—sequential analysis.

Llandough Hospital
Penarth, Glamorgan, Wales

1666 Feasby, R. E. Methyldopa and depression. *British Medical Journal*, 1(5325):261-262, 1963. (Letter).

Two cases of adverse effects with α -methyldopa therapy in carcinoid patients are reported. The α -methyldopa was used to control typical carcinoid flushes. Both cases developed motor retardation, and one case showed marked psychic disturbance with time disorientation. Symptoms were reversible when the drug was discontinued. The use of α -methyldopa in the carcinoid syndrome should be restricted to patients who are hospitalized or under close medical supervision.

Medical University Polyclinic
Basel, Switzerland

667 Huxtable, Robert F. & Landwirth, Julius. **Diphenhydramine poisoning treated by exchange transfusion.** American Journal of Diseases of Children, 106:496-500, 1963.

case is reported of a 15-1/2-month-old girl who developed hyperactivity and muscle twitching one hour after ingesting an unknown number of diphenhydramine tablets. Upon admission to the hospital, she was having violent convulsions, and seizure continued despite administration of 50 mg diphenylhydantoin i.v. and 60 mg phenobarbital i.m. Other clinical manifestations of her reaction are reported. Relief was obtained with an exchange transfusion of 500 ml of whole blood via femoral cut-down over a 110-minute period. Oxygen was given by mask during the transfusion. Her condition improved progressively, and two months later her physical and mental states appeared normal to both mother and doctor. A general discussion of this type of patient follows the case report.

Los Angeles, California

668 Robinow, Meinhard. **Diphenylhydantoin hypersensitivity. Treatment with mercaptopurine.** American Journal of Diseases of Children. 106:553-557, 1963.

case history is reported of a 7-year-old girl with a severe, prolonged hypersensitivity reaction, (including hepatosplenomegaly, lymphadenopathy, fever, arthritis, urticaria, and rashes) presumably due to diphenylhydantoin. He was given diphenylhydantoin (0.1 g, then 0.05 g b.i.d.) for mild allergic symptoms; severe symptoms then developed and he was given prednisone (40 mg/day) in addition to the diphenylhydantoin. He responded well until the dosage of prednisolone was reduced, at which time reaction to diphenylhydantoin was suspected and its administration was discontinued. Since tapering the prednisone dosage again produced recurrence of symptoms, treatment with mercaptopurine (5 mg/day) was begun. Various dosages were tested, and it was found that a combination of 50 mg mercaptopurine and 5 mg prednisolone daily was a sufficient dose. Results with mercaptopurine were favorable, and today the disorder is much less acute, though not cured. The author also reports favorable results of the drug combination in a 7-year-old girl with severe eczema and eczema. It is suggested, however, that these drugs not be used when safer and more thoroughly tested drugs are effective.

Yellow Springs, Ohio

1669 Slawson, Paul F., Flynn, William R., & Kollar, Edward J. **Psychological factors associated with the onset of diabetes mellitus.** Journal of the American Medical Association, 185(3):166-170, 1963.

In an effort to study the psychological and environmental setting in which diabetes mellitus develops, 25 patients with newly discovered diabetes mellitus were studied. Only patients between the ages of 18 and 70 who had developed clinical diabetes within 6 months prior to contact were included in the study. Severity of diabetes was rated according to stability and insulin required, and each patient was asked to complete a personality inventory (MMPI), which was followed by personal interview. Special attention was paid to any loss in the patient's life around the time of the onset of diabetes. While the results of the study reveal definite evidence of depression with respect to established norms, they do not reveal that new diabetics, as a group, are more depressed than other hospitalized patients. Two representative case histories are summarized. This and other studies indicate that psychological stress is not a necessary etiological factor in diabetes, but, rather, may trigger the initial metabolic imbalance in predisposed individuals.

700 Westwood Boulevard
Los Angeles, California

1670 Dulfano, Mauricio J. & Segal, Maurice S. **Nikethamide as a respiratory analeptic.** Journal of the American Medical Association, 185(2):69-74, 1963.

The immediate response to nikethamide was studied in 15 patients with histories of chronic lung disease and showing signs of acute respiratory failure. The patients were divided into the following two main groups: Group A included 8 males and 3 females, 51 to 84 years of age, with chronic obstructive pulmonary disease and acute respiratory failure precipitated by acute respiratory infection; Group B included 3 obese males and 1 obese female 56 to 71 years of age, with acute respiratory failure and chronic pulmonary disease, but without evidence of acute respiration infection. Nikethamide was injected i.v. in a single dose at a rate of 4 ml/minute, and the doses varied from 4 to 22 ml with an average dose of 5 ml. A prolonged dose was given to seven patients after the single dose by slow i.v. drip at a rate of 20 to 40 drops/minute, and the maximal dose was 30 ml. Clinically, there was a noticeable

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increase in mental lucidity and respiratory drive. Laboratory studies showed varied degrees of arterial carbon dioxide tension decrease and oxyhemoglobin saturation. Hypoventilation induced by oxygen breathing was corrected by nikethamide. The average effective single dose varied between 5 and 8 ml, and the prolonged dose was found to sustain the effects of the single dose. Toxic effects were minimal and brief, and the ratio between therapeutic and toxic levels was good.

Tufts University School of Medicine
Boston, Massachusetts

- 1671 Myschetzky, Andrej & Lassen, Niels Alexander. **Urea-induced, osmotic diuresis and alkalization of urine in acute barbiturate intoxication.** Journal of the American Medical Association, 185 (12):936-942, 1963.

Urea-induced diuresis and alkalization of the urine was used for the treatment of severe barbiturate intoxication with compounds of slow spontaneous elimination. Three hundred milliliters of an electrolyte solution (40 μ eg/ml sodium lactate, 12 μ eg/ml sodium chloride, 12 μ eg/ml potassium chloride, and 100 μ eg/ml glucose) and 80 ml of urea solution (0.5 g/ml urea and 155 μ eg/ml sodium chloride) given to 57 patients initially were followed by a steady infusion period of 600 ml and 30 ml, respectively. The average duration of diuretic treatment was 42 hours and an average diuresis of 12.1 liters/24 hours was obtained. The elimination rate of the barbiturates from the blood, calculated in percent/24 hours, was as follows: allyl-isopropyl-barbituric acid (55%/24 hours), ethyl-phenyl-barbituric acid (36%/24 hours), diethyl-barbituric acid and allyl-isopropyl-barbituric acid (60%/24 hours), diethyl-barbituric acid (51%/14 hours), diallyl-barbituric acid (72%/24 hours), and ethyl-allyl-barbituric acid (64%/24 hours). Of these 57 patients, 54 survived and 3 died. No diuretic treatment was given 20 patients not in deep coma at admission. All of these patients survived. The elimination rate was much slower in this group. The duration of coma was reduced in the diuretic-treated patients, and the reduction depended on the barbiturate. Diuretic treatment was found to reduce mortality and frequency of tracheostomy to 50% of those in a control group (82 patients). It was concluded that this method, with small modifications, is applicable in the treatment of other diffusible drugs.

Bispebjerg Hospital
Copenhagen, Denmark

- 1672 Dean, Edward S. **Self-induced stramonium intoxication.** Journal of the American Medical Association, 183(11):882, 1963.

Hallucinatory effects can be produced by an old fashioned asthma remedy containing 50.4% stramonium and 4.5% belladonna preparation Asthmador). Case histories are given of three young men admitted to the hospital suffering from self-induced intoxication after taking Asthmador. Diagnosis was aided by signs of atropinism, which led to the confirming history of ingestion of Asthmador. Stramonium contains atropine, scopolamine, hyoscyne, and hyoscyamine; the victim of it is made stupid and confused or hallucinated and excited. In heavy doses, stramonium can produce coma, convulsions, and death.

San Francisco General Hospital
San Francisco, California

- 1673 Vandam, Leroy D. & Collins, Wylie L. **Recovery from acute phenobarbital intoxication after prolonged coma.** Journal of the American Medical Association, 184(3):239-241, 1963.

The recovery of a 39-year-old woman from acute phenobarbital intoxication after prolonged coma (about 192 hours) is reported. The blood serum barbiturate level was 18.8 mg/100 cc, systolic blood pressure was 100 mm Hg, and temperature was 100° to 102° F. Several drugs, sodium succinate (3.0 g, i.v.), nikethamide (0.4 g, i.v.), and ethamivan (500.0 mg, i.v.) failed to stimulate the patient. Tracheal suction and manual compression of the chest to stimulate coughing resulted in the recovery of copious secretions and large mucous plugs. A transfusion of 500 ml of whole blood was given on the fourth day. On the fifth day, the blood-serum barbiturate level had declined to 13.2/100 cc and on the sixth day to 8.2 mg/100 cc. On the eighth day, she spoke and recognized her surroundings. A peroneal nerve palsy resulting in left-foot drop was discovered on the first attempt to walk. She was discharged on the twentieth hospital day. Recovery was attributed to the relatively young age of the patient, the lack of complicating organic disease, and the excellent nursing care.

721 Huntington Avenue
Boston, Massachusetts

1674 Friedman, Arnold P., & Elkind, Arthur H. **Appraisal of methysergide in treatment of vascular headaches in migraine type.** Journal of the American Medical Association, 184(2):125-128, 1963.

Methysergide maleate (1-methyl-lysergic acid butanolamide) was given as a prophylactic treatment for 2.5 years to 421 patients with vascular headaches of the migraine type. The patients were divided into two main groups: Group 1, 258 who were treated from 2 to 30 months; and Group 2, 163 who were treated for less than 2 months. Methysergide maleate or placebo was given in doses ranging from 6 mg/day in three divided doses to 16 mg/day. Sixty-one of the patients of Group 1 received placebo and 118 received the drug. Methysergide maleate reduced the frequency of headaches by at least 50% in the 118 patients, a result significantly better than the placebo response. Of the 163 patients treated for less than 2 months, 15 improved on administration of methysergide maleate. Side effects were frequent but usually mild, and adjustment of dosage was necessary. It was concluded that methysergide maleate had no value in treating the acute attack, but is effective in the prophylactic treatment of all forms of migraine headache.

Columbia University
New York, New York

1675 Possel, H. **Omnisedan in der internen Fachpraxis.** (Omnisedan in internal medicine.) Medizinische Welt, 13:205-206, 1963.

Over a 1-year period, the mild sedative omnisedan (0.1 g methylpentynol, 0.1 g bromo-sovalerianylcarbamide, and 0.075 g meprobamate per capsule) was given to 175 patients, including: (1) 75 patients with vegetative dystonia; (2) 25 patients with cardiovascular sensations of various kinds; (3) 50 patients with symptoms resembling hyperthyrea; and (4) 25 patients with cervical or lumbar syndrome. The 4-week course of treatment is described. After 14 days of treatment, all subjective cardiovascular complaints disappeared in 20 patients in group 2, and the other 5 patients showed improvement. Only one patient still had symptoms at the end of treatment. In group 1 mild to moderate tachycardia was normalized in 14 days, hyperhidrosis improved, though more slowly, and within 3 weeks 38 patients were completely symptom free. No lapses have occurred. In patients of

group 4, improvement was due to the relaxant effect of meprobamate on the striated musculature. Within 3 weeks, 12 patients were symptom free, medico-mechanical measures eliminated residual symptoms in 6 others, and 6 patients were unchanged. A temporary dosage increase to 2 capsules t.i.d. produced additional improvement in the last two groups. No side effects were noted, and there was no reaction to abrupt drug withdrawal.

Munich, Germany

1676 Keitel, Peter. **Klinische Untersuchungen zur neuroleptischen Wirksamkeit von Triperidol.** (Clinical investigations of the neuroleptic efficacy of triperidol with special attention to the extrapyramidal fine motor apparatus.) Medizinische Welt, 26(26):1380-1384, 1963.

The neuroleptic effects of triperidol in varying doses were studied in experiments in 20 female, schizophrenic patients over a 3-month period. Each patient was examined daily for extrapyramidal fine motor responses. The essential antipsychological activities reacted first, after which handwriting changes and hypokinetic effects appeared. By the fourth day of treatment, all patients demonstrated a fine motor extrapyramidal hypokinesia, and by the end of the first week, triperidol had reached its full antipsychotic efficiency. Within 4 weeks, optimal therapeutic effects were demonstrated in 15 of the 20 cases. For neuroleptic efficiency, the daily dosage appeared to be 0.5 to 1.5 mg. The appearance of greater motor extrapyramidal symptoms indicates overdosage, and medication should be withheld until the fine motor (handwriting) extrapyramidal symptoms reappear.

Psychiatric Clinic of the Medical College
Rhein State Hospital
Dusseldorf, Germany

1677 Šercl, M. & Kovařík, J. **Über die Beeinflussung der Charcotschen Krankheit mit Centrophenoxin (ANP 235, Lucidril).** Studie über die amyotrophische lateralsklerose XIII. (The effect of centrophenoxine (ANP 235, Lucidril) in Charcot's disease. Study of amyotrophic lateral sclerosis XIII. Psychiatria et Neurologia, 146:55-63, 1963.

A test was made comparing centrophenoxine and trypan red in two groups of 13 patients each, with various stages of Charcot's

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disease. Both groups included nine men and and four women with mean age between 50 and 60. The effect on amyotrophic lateral sclerosis was used as the index of drug action. The daily dosage of centrophenoxine was 0.1 to 0.3 g p.o. or 0.25 g via injection. At the end of therapy, improvement (I), worsening (W), or no change (N) was observed in the following numbers of patients: subjective symptoms--I 4, W 2, N 7; objective symptoms--I 4, W 0, N 9. Followup treatment and observation for 1/2 to 1 year showed lasting improvement in none of the patients; six patients were unchanged, data were not available on three patients, and four patients had died. All patients, including those in advanced stages of the disease, showed good tolerance for centrophenoxine. The second group received a total dose of 90 to 100 ml of 1% trypan red solution, i.v. Of this group, five patients showed improvement, none worsened, and eight were unchanged. After 6 weeks' to 9 months' followup treatment, no patients showed lasting improvement; six were unchanged, no data were available on three patients, and four patients had died. Empirical comparison and statistical evaluation of the therapeutic results using the chi square test showed no advantage of centrophenoxine over trypan red.

Charles University
Hradec Kralove, Czechoslovakia

1678 Helmchen, Hanfried. Über zentralnervöse Dekompensation bei psychiatrischer Pharmakotherapie als Beitrag zur experimentellen Psychiatrie. (Central nervous decompensation in psychiatric pharmacotherapy as a contribution to experimental psychiatry.) Fortschritte der Neurologie, Psychiatrie und Ihrer Grenzgebiete, 31(3): 161-175, 1963.

A short history of studies in central nervous decompensation and a theoretical model of the syndrome are presented. Clinical examples in which the syndrome appears in conjunction with psychiatric pharmacotherapy demonstrate that drug therapy is a method in which definite efficiency and greater controls are demanded. Only when conclusions on the experimental aspects of the therapy be drawn. Individual characteristics must be comprehended factors, systematic observations of the decompensation process must be described, and concrete clinical phenomena must be exemplified. Decompensation must be understood as a

definite peculiarity of the physical structure of the individual, especially demonstrated as atypical, unexpected, or paradoxical therapy effects. In clinical examples, the manner in which individual factors can be assembled has been demonstrated, and the clinical picture has been clearly unfolded. (111 references)

Berlin Free University
Berlin, Germany

1679 Stephan, H. J. Erfahrungen in ambulanter Praxis mit Triflupromazine. (Experiences with triflupromazine in out-patient practice.) Medizinische Welt, 12(12):645-647, 1963.

Experience with the neuroleptic triflupromazine in psychiatric outpatients is reported. Triflupromazine has a wide spectrum of action, and is used to treat disorders ranging from psychosomatic illness to endogenous and exogenous psychoses; it is a potent antiemetic. The drug dulls the emotions without affecting intellectual performance, which makes it suitable for ambulatory patients. From the beginning of treatment, the drug produces undesirable side effects, primarily rashes. Nevertheless, the drug produces definite changes in the course of illness, appearing in the mental attitude of the patient, and his will to live.

University of Münster
Münster, Germany

1680 Flegel, Horst. Verlaufsrepräsentation als Korrektiv für die Erfolgsbeurteilung der Schizophreniebehandlung. (Graphic representation of clinical course as a corrective measure for judging the efficacy of treatment of schizophrenia.) Psychopharmacologia, 5:16-17, 1963.

Quantitative representation of clinical efficacy was demonstrated during a trial of fluphenazine in schizophrenics. After the degree and time of improvement of the target symptoms are plotted graphically, the area under the curve is measured with a planimeter. When the numerical value representing the best previous improvement is divided by the value representing the effect of the drug currently being tried, an index of therapeutic efficiency is obtained. This method permits comparison of two or more drugs used in the same case.

Rhine State Hospital
Dusseldorf, Germany

1681 Pöldinger, Walter. *Klinische Erfahrungen mit dem Librium-Analogen Ro 5-2807 (Valium) bei psychotischen Zustandsbildern.* (Clinical experiences with the Librium analogue Ro 5-2807 (Valium) in psychotic states. *Schweizer Archiv für Neurologie, Neurochirurgie und Psychiatrie*, 12(2):510-514, 1963.

In clinical experiments with 47 schizophrenic patients with varying manifestations, tablets of diazepam of 5- and 10-mg strengths were given orally to 19 patients for 4 months, and 29 patients were started on i.m. injections for 6 to 10 days and then given tablets p.o. Results, compared with similar experiments with chlordiazepoxide, show that diazepam demonstrates a stronger neuroleptic action. Diazepam proved to be effective in the treatment of schizophrenic psychoses, especially the paranoid-hallucination conditions. Diazepam did not show the beneficial effects previously found with chlordiazepoxide in the treatment of alcoholic psychoses. The positive action of chlordiazepoxide in anxiety states was not observed in results of similar treatment with diazepam. Since only 47 patients were used, findings should be regarded as first impressions.

St. Urban's Psychiatric Clinic
Lucerne, Switzerland

1682 Meusert, W. *Erfahrungen mit einem neuen psychotropen Präparat aus der Librium-Reihe (Ro 5-2807, Valium).* (Experiences with a new psychotropic drug of the Librium series (Ro 5-2807, Valium). *Deutsche Medizinische Welt*, 34(34):1680-1683, 1963.

A clinical study of the use of diazepam, a benzodiazepam derivative, in the treatment of 267 ambulatory patients with neurotic and vegetative disorders was carried out over a 2-year period. Results showed that the medication had considerable effect in anxiety and antidepressive states. Personality disorders, in spite of various other psychopharmacological and psychotherapeutic measures, show a high average percentage of improvement with diazepam. No observations were made in related disorders regarding medication over an extended period (one isolated case of over 2 years). It can be stated that there is definitely a favorable therapeutic value in diazepam as compared with results in the use of chlordiazepoxide. The therapeutic effects of diazepam surpass those of chlordiazepoxide.

Remberg, Germany

1683 Sanchez-Salazar, Anibal A., Pembleton, Williams E., & Banerjee, Chandra M. *Doxapram hydrochloride as a respiratory stimulant in anesthetized man.* *Anesthesiology*, 24(6):808-812, 1963.

To determine the usefulness of doxapram HCl in the treatment of respiratory depression due to general anesthesia, seven adults (hospitalized for elective surgical procedures) were given the drug. Following surgery, the patients, under thiopental anesthesia (31 mg/kg), were taken to a recovery room where they were allowed to breathe room air for 20 minutes. Arterial blood samples were taken, and when the patient's condition was stable (i.e., unchanging EEG level and stable clinical signs), doxapram HCl was injected i.v. in single doses of 0.5 or 1.0 mg/kg. At each dose level, patients were tested for tidal volume, respiratory rate, minute ventilation, PO_2 and PCO_2 , hydrogen ion concentration, and blood pressure and pulse rate. At both doses, brief respiratory stimulant and arousal effects of doxapram HCl were demonstrated in all seven patients. The most marked effect was an increase in tidal and minute volume with a rise in arterial PO_2 , a fall in PCO_2 , and a rise in pH at both doses. There was a significant increase in heart rate at 1.0 mg/kg only, and no changes in EEG, ECG, or blood pressure were observed at either dose.

Medical College of Virginia
Richmond, Virginia

1684 Sussman, Sidney. *Narcotic and methamphetamine use during pregnancy. Effect on newborn infants.* *American Journal of Diseases of Children*, 106:325-330, 1963.

Observations of diacetylmorphine (heroin) addiction and methamphetamine habituation in pregnant mothers and their infants are discussed. Nineteen mothers, most of whom were not married and had no prenatal care, and their 12 premature and 11 full-term infants were studied. Twelve mothers had used diacetylmorphine alone, three used diacetylmorphine with codeine, one used diacetylmorphine with codeine and barbiturates, and four were habituated to methamphetamine. On admission, five showed signs of recent narcotic use and five had withdrawal symptoms in the postpartum period. Six infants were born in the breech position, 11 had respiratory distress and 17 had withdrawal symptoms, which

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included CNS, gastrointestinal, or respiratory disturbance. The most common withdrawal symptoms were convulsions, jitters, hyperactivity, tremors, excessive irritability, regurgitation, yawning, and sneezing. Swaddling and demand feeding controlled these symptoms in most infants. Development of withdrawal symptoms is correlated with the narcotic dose and the time interval between the last injection and delivery. Follow-up in 10 infants revealed normal physical and mental development in 9 and mental retardation in 1.

San Francisco General Hospital
San Francisco, California

- 1685 Rudolf, G. de M. **Persistence of barbiturates.** British Medical Journal, 2(5367):1268, 1963. (Letter).

In a comment on an article (September 1963 issue) on the persistence of barbiturates that concluded that there was little or no evidence to justify the use of a sedative night after night for insomnia, the author states that one of the references used to formulate the opinion expressed in the article actually contradicts the conclusion. The reference says that barbiturates have no follow-on effect from night to night.

Mount Pleasant Nursing Home
Clevedon, Somerset, England

- 1686 Milner, G., Kumar, K., Bakker, A. H., & Landa, A. **Drugs for depression.** British Medical Journal, 1(5339):1231, 1963. (Letter).

Comments are made on an article (January 19 issue) on the value of drugs in depressive illnesses. A recent survey indicated a significant decrease in the number of patients suffering from severe depression who required admission. The increased use of antidepressants and the awareness of the general practitioner in the early diagnosis of a depressive illness have contributed to this decline in admissions.

The Towers Hospital
Leicester, England

- 1687 Ruddell, J. Shegog. **An antagonist to suxamethonium bromide.** Lancet, 1(7286):889, 1963. (Letter).

Trifluoperazine, when administered 1 to 2 mg i.m., reverses apnea caused by suxamethonium bromide in patients anesthetized with methohexitone sodium and maintained on nitrous oxide. Laboratory findings suggest that the action of trifluoperazine occurs at the cell membrane or synapse level, and the drug seems to be independent of the pseudocholinesterase concentration which is unaltered by the drug.

Lethbridge, Alberta, Canada

- 1688 **Safety of non-barbiturate hypnotics.** British Medical Journal, 1(5322):41, 1963.

The safety of any drug is judged first on the difference between the mean therapeutic dose and the mean dose which gives rise to definite toxic effects or death. On this basis, all the nonbarbiturate hypnotics at present in common clinical use can be regarded as safe. The second requirement is that when the drug is given in the accepted therapeutic dosage the incidence of side effects should be low and they should not be of a serious nature. Side effects of nonbarbiturate hypnotics are of only minor significance in most cases. One of the safest is chloral hydrate and its derivatives, dichlorophenazone and trichlorethyl phosphate. No serious effects have been reported with methypylone, methaqualone, and ethchlorvynol. Although glutethimide has a similar chemical structure to thalidomide, it has not been shown to have teratogenic effects. The danger of habit formation and addiction probably exists with any sedative or hypnotic drug.

(No address)

- 1689 Iasagna, Louis. **Actions of barbiturate.** British Medical Journal, 2(5370):1467-1468, 1963. (Letter).

In commenting on an article that stated that barbiturates were not satisfactory as routine hypnotics in elderly patients because of the high incidence of side effects, the author points out that this conclusion was based on experiments with only one barbiturate, amylobarbitol. Results for one barbiturate cannot be assumed to be true for other barbiturates.

The Johns Hopkins Hospital
Baltimore, Maryland

1690 Bloom, Philip M. Increased libido with chlorprothixene. *British Medical Journal*, 2(5369):1406, 1963. (Letter: comment on letter by G. Sedman.).

In commenting on a letter (October 19 issue), the writer points out that increased libido is not necessarily a drug effect, but that the drug acts, rather, as relief from guilt for a patient with morbid masturbation guilt.

London, W.1, England

1691 Craig, D. D. H. Chlorphentermine. *British Medical Journal*, 2(5367):269, 1963. (Letter).

This letter protests a reference made to chlorphentermine (October 5 issue) in which it was stated that chlorphentermine produces central nervous stimulation while suppressing appetite. The author is not aware of any other reports of this kind.

William R. Warner & Co. Ltd.
Barnstaple, England

1692 Hobbs, J. J. Drugs for depression. *British Medical Journal*, 2(5364):1067, 1963. (Letter).

The author comments on a panel discussion on Drugs for Depression (September 28 issue), stating that only a small portion of patients seen in general practice have severe depressions. The "minor depression syndrome" is the commonest form of depression seen in general practice. Its constituent symptoms are depressed mood, lack of energy, inability to concentrate, and irritability. The importance of the doctor's personality in effectively treating the patient is discussed. Placebo is used indiscriminately to mean the true placebo and the dummy treatment.

Whittington, Northumberland, England

1693 Exton-Smith, A. N., Hodkinson, H. M., & Cromie, B. W. Controlled comparison of four sedative drugs in elderly patients. *British Medical Journal*, 2(5364):1037-1040, 1963.

The hypnotic effects of amylobarbitol sodium (200 mg), dichloralphenazone (1.3 g), promazine resinate (50 mg), meprobamate

(800 mg), and a placebo were compared in a blind controlled trial using 65 elderly, female patients from a geriatric ward. The four drugs and placebo were each given for one night from Monday to Friday in a random order, using a Latin-square design. The night staff of the ward made hourly assessments of the patients' sleep, and, in the morning, the patients were asked for an overall evaluation of their night's rest. Results indicate that, at the dosages used, all four drugs were of similar effectiveness in producing sleep, but that meprobamate and dichloralphenazone have properties, such as lack of morning drowsiness, that account for the patients' particular preference for them. Methods of sequential and qualitative analysis of the comparison are described.

The Whittington Hospital
London, England

1694 Lysergic acid in treatment of neuroses. *British Medical Journal*, 2(5349):106, 1963.

LSD-25, a potent hallucinogen, has also been used as an abreactive agent in the treatment of certain types of neurosis. In general, anxiety and tension of recent onset respond best to LSD therapy. The only controlled trial so far reported stated that LSD is no more effective than standard psychotherapy or abreaction with intravenous methylamphetamine and hexobarbital. The LSD-25 is usually given 0.1 to 0.2 mg p.o. A reaction develops 30 to 60 minutes later and begins to subside after about 6 hours. The effects can be abolished by administering chlorpromazine 50 mg i.m. or 100 mg p.o.

(No address)

1695 Matthews, A. E. B. Double-blind trials of promazine in labour. *British Medical Journal*, 2(5354):423-427, 1963.

Two controlled, double-blind clinical trials of the use of promazine in treating the fear and anxiety which accompany labor are described. In the first study, the condition of the mother in labor was assessed, whereas the second study consisted of an assessment of drug effects. A preliminary trial had assured the safety of promazine administration. In both trials, all patients were given pethidine for pain relief in addition to promazine (about 500

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patients) or in addition to placebo (about 500 patients). In the first trial, midwives were asked to classify the mental state of the patient on admission, during the first stage of labor, and during the second stage of labor. Their evaluation and an assessment after delivery of labor pain by the mothers failed to show any difference between the control and the promazine group. In the second trial, the midwife giving the medication returned 45 minutes after each administration to assess the drug response. In this way, there was a single observer, and other factors such as the variable lengths of labor and the traditional timing of drug administration were of no importance in the assessment of results. The promazine group showed a significant increase in the percentage of patients with marked improvement of mental state and pain at all dosage levels tested. It was concluded that promazine is a useful adjunct to therapy in labor.

West Middlesex Hospital
Isleworth, England

- 1696 Parsons, T. W. Clinical comparison of barbiturates as hypnotics. *British Medical Journal*, 2(5364):1035-1037, 1963.

A total of 173 patients (91 men and 82 women) who had previously benefited from a hypnotic, participated in a series of six trials devised to compare the hypnotic effects of phenobarbital, butobarbital, and quinalbarbital. Each trial consisted of a comparison of two of the three drugs by administering the drugs at bedtime, one drug being given on the first night, the other on the following night. In the morning after the second hypnotic, each patient was questioned. The first trial showed that quinalbarbital (100 mg) was superior to be an inert tablet; the second trial demonstrated no important difference between 100 mg of quinalbarbital and 100 mg of phenobarbital; the third trial showed no important difference between 100 mg butobarbital and 100 mg of quinalbarbital; the fourth trial showed 200 mg of quinalbarbital to have superior hypnotic effect compared with 200 mg of phenobarbital, the fifth trial showed 200 mg of butobarbital to be more effective than 200 mg of phenobarbital, and the sixth trial demonstrated the superior hypnotic action of 200 mg of quinalbarbital compared with 200 mg of butobarbital. At 200 mg, the drugs in

descending order of effectiveness were: quinalbarbital, butobarbital, and phenobarbital.

Western Infirmary
Glasgow, Scotland

- 1697 Svendsen, B. Borup & Willadsen, J. The use of haloperidol (Serenase) in chlorprothixene resistant patients. *Acta Psychiatrica Scandinavica*, Trans. Suppl. 169(39):351-355, 1963.

Results of the use of haloperidol in chlorprothixene-resistant patients, who were treated in a clinic from January 1961 to May 1962, are reported in a series of tables that indicate: age and sex of the patients, duration of haloperidol treatment, dosage of haloperidol, diagnoses of the patients and effect of haloperidol therapy, reason for withdrawal of haloperidol, and side effects of the therapy. It was concluded that haloperidol has been of benefit to a fair number of the tested patients, and the side effects, though disturbing, were not serious.

Rigshospitalet, Psychiatric Clinic
Copenhagen, Denmark

- 1698 Davies, T. S. & Leyshon, M. W. Ospolot in epilepsy. *Lancet*, 2(7314): 939-940, 1963. (Letter).

A trial study is presented of a group of epileptic, mentally subnormal patients given tetrahydro-2-p-sulphamoylphenyl-1,2 thiazine, 1,1-dioxide (Ospolot) 0.1 g b.i.d. for a week; the dosage was gradually increased to 0.2 g t.i.d. No side effects were observed. This drug was added to their previous medication of phenobarbital and/or sodium phenytoin. When phenobarbital and/or sodium phenytoin was suddenly replaced by Ospolot, the number of fits increased, but the addition of Ospolot to the previous medication usually caused a reduction. The total number of grand-mal and petit-mal attacks decreased 50%.

Llanfrechfa Grange Hospital
Cwmbran, Wales, Great Britain

699 Montuschi, E. & Robinson, D. K. Pargyline hydrochloride in hypertension. *Lancet*, 2(7320):1280-1281, 1963. (Letter).

The case of 20 hypertensive patients (13 females, 7 males) treated with pargyline hydrochloride are reported. Pargyline 25 mg/daily p.o.) showed a hypotensive effect (except in two patients) in 2 or 3 weeks after the beginning of treatment. The mode of action appeared to be through adrenergic blockade, giving rise to orthostatic hypotension. A mild antidepressive action was observed; side effects were few, and toxic effects were absent.

Whittington Hospital
London N.19, England

700 Aladjemoff, Leonie, Weinberg, Haim, & Alkalay, Isidor. Fat-embolism. Treatment with lytic cocktail and surface cooling. *Lancet*, 2(7297):13-15, 1963.

Our patients with fat embolism were treated with lytic cocktail (100 mg promethazine and pethidine and 50 mg chlorpromazine diluted in 100 ml of normal saline solution) by i.v. drip for 20 to 30 minutes, and surface cooling was achieved by alcohol sponging and cool air. Tracheostomy was performed as soon as possible for the prevention of pulmonary infection. Acute dilatation of the stomach was prevented, and gastric absorption of fluids was improved by lavage with Ringer's solution. Two of the patients (male, 33 and 36 years of age) died, and postmortem examination revealed fat-embolism in the heart, brain, and kidneys, as well as lung edema, pneumonia, and jaundice. The two surviving patients (one male, 33 years; one female, 35 years) could only swallow teaspoonfuls of liquid without aspirating, and decanulation and closure of the tracheostomy were done only after the patient could drink freely without aspirating. As the patients improved, progressively smaller amounts of cocktail were needed to keep the temperature steady at the intended range 36° to 35° C).

Hadassah University Hospital
Jerusalem, Israel

1701 McAllister, Donald. Prevalence of common menstrual symptoms. *Lancet*, 2(7303):360, 1963. (Letter).

In a letter to the editor, it is reported that a new compound, diazepam, is being studied for its relief of dysmenorrhea. Due to its antianxiety and uterine-muscle-relaxant activity, the results in 20 patients have been very encouraging.

Mosgiel, New Zealand

1702 Splitter, Samuel R. Comprehensive treatment of office patients with the aid of a new psychophysiologic agent, opipramol (Ensidon). *Psychosomatics*, 4:283-289, 1963.

To test the antianxiety and antidepressant properties of opipramol, a double-blind study was conducted on 100 outpatients (38 male and 62 female, 15 to 87 years of age) who, though their symptoms varied, all showed some degree of depression and anxiety. Psychotherapy accompanied treatment. Fifty patients received placebo and 50 patients received 50 mg opipramol q.i.d. Patients were seen once a week, and both objective and subjective response of all target symptoms, as well as improvement of any somatic disorder, was recorded and evaluated weekly over a 6-week period. While 42 patients in the placebo group did not improve, 47 of the 50 patients receiving opipramol showed either excellent or good results. Side effects were preponderant in the placebo group (39 patients), but only 8 patients in the opipramol group reported side effects (drowsiness and dry mouth). Four case histories are reported.

Hempstead Medical Center
Hempstead, New York

1703 Segal, Andrew E. & Rogin, James R. Dyshidrosis; a dual therapeutic approach. *Skin; Dermatology in General Practice*, 2:223-225, 1963.

Chlordiazepoxide and clidinium bromide in a single capsule was administered to patients with dyshidrosis for the dual purpose of relieving hyperhidrosis and any

anxiety and tension operative in the formation of the dyshydrotic process. Sixty-five patients (34 males and 31 females), ranging in age from 6 to 70 years, were given the capsule (5 mg chlordiazepoxide and 2.5 mg clidinium bromide) orally q.i.d. Three patients had neurodermatitis, 59 had dyshydrotic eczema, and 3 had hyperhydrosis associated with increased anxiety and tension. Marked improvement in the dermatosis was shown by 42 of the patients with dyshydrotic eczema, while 17 showed no improvement. Relief of emotional symptoms was observed in 47 patients, while 12 had no significant relief. Marked improvement in both emotional and dermatological symptoms was shown by the six patients of the two other groups. Recurrence of the eczema was prevented for 1 to 4 months in 14 patients, and prompt reinstitution of the drug upon onset prevented the disease in 23 patients. Drowsiness (2 patients), blurred vision (1 patient), and increased nervousness (1 patient) were the side effects encountered. With the exception of corticosteroid treatment, this combination seems to be an improvement over any other treatment.

Wayne State University
Detroit, Michigan

See also: 1621, 1623, 1624, 1630, 1633,
1634, 1639, 1640, 1642, 1644, 1646, 1652,
1653, 1654, 1655, 1708, 1710, 1776

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704 Mark, Harry H. **Psychotogenic properties of cyclopentolate.** Journal of the American Medical Association, 186(4): 430-431, 1963.

The psychotogenic properties of cyclopentolate HCl and the similarity of this drug to well-known psychoactive compounds were illustrated in this study of four cases. The eyes of the subjects (3 males, 5, 6, and 72 years of age and 1 female, 14 years of age) were instilled with a 1% or 2% solution of cyclopentolate after which a schizophrenia-like behavior pattern associated with ataxia was observed. The severity of the reaction varied and was observed in only a few subjects, indicating idiosyncrasy on the part of the subject. This compound resembles lysergic acid, diphenine, and many piperidyl benzilate compounds in its psychotogenic properties. In two of the six cases reported thus far, there is some history of brain damage that may prove significant in the production of the psychotic reaction to cyclopentolate.

100 York Street
New Haven 11, Connecticut

705 Isbell, Harris. **Drug addiction.** Journal of the American Medical Association, 186(12):1112, 1963.

Pentazocine is reported to be nonaddicting; the validity of this statement is questioned, since pentazocine is a centrally acting analgesic. In the reply, it is stated that the generalization that any drug relieving pain by central action is potentially addicting is true only for substances with pharmacological effects similar to morphine. Pentazocine differs pharmacologically from morphine. Methods for assessing the addictiveness of new drugs are described, and results of such testing with meperidine, dextromoramide, dextromethorphan, dextropropoxyphene, and the combination of pentazocine and diphenoxylate are reported. Studies have shown that pentazocine does not produce morphine-like subjective effects; its addictiveness is judged to be lower than that of codeine.

Cincinnati, Kentucky

1706 DuBois, Kenneth P. **Drug-induced depression of central nervous system.** Journal of the American Medical Association, 186(2):174, 1963.

The case of a patient who died in circulatory collapse after the ingestion of 40 to 60 mg prochlorperazine and about 80 ml paraldehyde was cited when the question of whether these drugs have an additive depressant effect was posed. In answer to this question, it was stated that both drugs produce CNS depression and cardiovascular effects; therefore, an additive action could be expected. The central depressant action and the cardiovascular actions of paraldehyde could have been potentiated by prochlorperazine.

Chicago, Illinois

1707 Brandon, Synney. **Addiction to amphetamines.** British Medical Journal, 2(5366): 1204, 1963. (Letter).

In a survey conducted by general practitioners, nearly one in five of those patients receiving amphetamines were shown to be habituated. Apart from the doubtful therapeutic necessity for these drugs, there appears at times to be a carelessness in their prescription that amounts to real negligence.

Columbia University College of Physicians and Surgeons
New York, New York

1708 Reynolds, Telfer B. & Edmondson, Hugh A. **Chronic renal disease and heavy use of analgesics.** Journal of the American Medical Association, 184(6):435-444, 1963.

Eight cases, 2 male and 6 female ranging in age from 24 to 64 years, suffering from chronic renal disease with a long history of

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heavy use of analgesics containing phenacetin (acetophenetidin) are described. The patients were observed over a 3-year period. The admitted phenacetin consumption ranged from 1 to 5 g daily over many years with an ingestion pattern suggesting habituation or addiction. Headache was the outstanding symptom in seven of the eight patients. Hyperazotemia, papillary necrosis, and evidence of urinary-tract infection were the prominent clinical features. Other symptoms present include hypertension, anemia, and bacteriuria. Three of the patients died of uremia. Pathologic findings were severe papillary necrosis without extensive polymorphonuclear exudate, interstitial fibrosis with remarkable atrophy of tubules and peritubular capillaries in the medulla, focal areas of tubular atrophy in the cortex, and increase in round cells and fibrous tissue in the interstitium. These changes were felt to be unique, recognizable, and different from those caused by pyelonephritis alone.

University of Southern California
School of Medicine
Los Angeles, California

- 1709 Saunders, John C. & Barsa, Joseph A.
Oral hormone testing of pseudo-pregnancy induced by phrenotropic drugs. *Journal of the American Medical Association* 184(12):974-976, 1963.

The possible effects of phrenotropic (psychotropic) drugs on the ovarian cycle and on response to a hormone preparation used for diagnosing pregnancy were studied in 27 nonpregnant, female psychotic patients (18 to 41 years of age). They had been hospitalized continuously for 2 to 13 years, had been receiving phrenotropic drugs for 2 to 6 years, and had had amenorrhea from 4 months to 6 years. Their phrenotropic drug regimen was continued during administration of a 2.5 mg norethindrone acetate and 0.05 mg ethinyl estradiol preparation in tablet form. In patients who failed to menstruate after the standard test dose (1 tablet b.i.d. for 2 days), half received the same dose and half received an increased dose of two tablets b.i.d. for 2 days the following month; patients who failed to respond on this regimen were given four tablets b.i.d. for 2 days a month later. There were 15 false positive reactions (failure to menstruate) in the first trial; 5 of 8 receiving the

double dose had a false positive reaction, and 10 of 13 given four tablets continued to give a false positive reaction. Animal studies reviewed indicate that phrenotropic drugs release luteotrophic gonadotrophin from the anterior pituitary which maintains the functional capacity of the corpus luteum. It is postulated that a functional corpus luteum produces pseudopregnancy, because there may be a return to the normal menstrual cycle if the phrenotropic drug is discontinued or if the norethindrone acetate--ethinyl estradiol mixture is given in sufficient dosage. The effect of estrogen and progesterone in the human may be partially mediated in specific areas of the CNS affected by phrenotropic drugs.

Rockland State Hospital
Orangeburg, New York

- 1710 Harville, Donald D. & Summerskill, William H. J. Surgery in acute hepatitis. Causes and effects. *Journal of the American Medical Association*, 184(4): 257-261, 1963.

A review is presented of the causes and effects of surgery in acute hepatitis in 42 patients (26 males and 16 females) with viral hepatitis (32 presumed to have infectious hepatitis and 10 presumed to have serum hepatitis) and 16 patients (6 males and 10 females) with drug hepatitis (presumably from former treatment with chlorpromazine, methyltestosterone, or chlorpropamide). Reason for surgery in 50 of the 58 patients was suspected extrahepatic biliary obstruction. The results of several tests including hepatic function and liver histology are included, and the most prominent symptoms prior to operation were anorexia, malaise, and jaundice. In the 42 cases of viral hepatitis, there were four fatalities within 3 weeks of operation, and in 5 others there were major complications (paralytic ileus, pulmonary embolism and wound dehiscence, subphrenic abscess and sinus tachycardia, progressive hypoalbuminemia with ascites, and perforation of an ileoileal stoma). One fatality and one major complication occurred among the 10 patients with serum hepatitis, and all other complications occurred in the 32 patients with infectious hepatitis. No deaths or serious complications occurred in patients with drug hepatitis.

Mayo Clinic
Rochester, Minnesota

- 1711 Sargent, William. Combining the antidepressant drugs. *Lancet*, (7308):634-635, 1963. (Letter).

It has been found possible in actual practice to treat hundreds of patients with combinations of the MAO inhibitors, such as iproniazid or phenelzine, together with imipramine or amitriptyline. The two groups can be safely used one after the other or before the other with no long interval between them. It is true that hypotensive reactions are more common, and severe temporary falls in blood pressure and occasionally fevers can occur. Dosages should be watched carefully. Dangers and even fatalities can occur if MAO inhibitors are combined with intravenous amphetamine or methylamphetamine, though apparently they can be safely used with "Drinamyl" taken orally, though this contains dexamphetamine plus amylobarbitol.

St. Thomas's Hospital
London, S.E.1, England

- 1712 Waghmarae, D. Collapse after pethidine and promethazine. *British Medical Journal*, 2(5362):936, 1963. (Letter).

Two patients who had passed their expected dates of delivery by 14 days were given intramuscular injections of a combination of pethidine and levallorphan (100 mg) and promethazine HCl (25 mg) preparatory to artificial rupture of the membranes for induction of labor. The first patient (4 years old) became pale and pulseless with unrecordable blood pressure approximately 5 minutes after the injection. She was given oxygen by mask and by the time intravenous infusion was started improvement in her condition was marked. The second patient (28 years old) suffered the same reaction and recovered as quickly. Both babies were healthy and cried immediately after delivery. Although the combination of pethidine with levallorphan and promethazine HCl has been used for sedation and analgesia in well over 200 cases before and during labor, no ill effects have been observed apart from the cases described.

St. Khan Platinum Jubilee Hospital
Nairobi, Kenya, Africa

- 1713 Hurding, Roger F. & Missen, Hedley J. Reactions to tranlycypromine. *British Medical Journal*, 2(5362):936-937, 1963. (Letter).

A case of subarachnoid hemorrhage due to tranlycypromine is reported in a 62-year-old woman. The patient had a long history of neurotic depression and vertical headaches, and had been taking trifluoperazine (1 mg b.i.d.) for 3-1/2 years. The medication was stopped, and a tranlycypromine--trifluoperazine combination was substituted. On the sixth day of taking this combination, the patient's customary headache became worse, and the tablets were stopped. Five days later there was marked neck stiffness, a positive Kernig's sign, and a low-grade pyrexia; blood pressure was 170/110 mm Hg but there was no retinopathy or sign of congestive heart failure. A lumbar puncture revealed xanthochromia. It is believed that this is the first recorded instance of bleeding substantiated by lumbar puncture, although signs simulating those of subarachnoid hemorrhage seem to be quite common with tranlycypromine therapy.

Chelmsford, Essex, England

- 1714 Roebuck, Basil E. Diethylpropion and addiction. *British Medical Journal*, 2(5362): 936, 1963. (Letter).

The weight of presently available evidence indicates that the amphetamines, phenmetrazine, and diethylpropion hydrochloride are safe, effective, and useful when given under proper medical supervision according to the manufacturers' directions. Observations from a mathematically minuscule number of cases scarcely warrant the conclusion that a drug is addictive and do not provide convincing evidence that it is dangerous.

The Wm. S. Merrell Company
Cincinnati, Ohio

- 1715 Berger, F. M. Side-effects of meprobamate. *British Medical Journal*, 2(5362):936, 1963. (Letter).

No case of agranulocytosis has been described in patients receiving only meprobamate. There were three cases in

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patients who, in addition to meprobamate, received a drug of the phenothiazine or imipramine group. A case of aplastic anemia after meprobamate was described, but the patient was also receiving sulfonamide nose drops, Coricidin (containing chlorpheniramine maleate, aspirin, phenacetin, and caffeine), as well as various hormones which may well have been responsible for the occurrence of aplastic anemia. The incidence of side effects with meprobamate (widely prescribed since 1955) appears to be lower than with any other widely used tranquilizer.

Wallace Laboratories
Cranbury, New Jersey

- 1716 Giles, H. McC. Imipramine poisoning in childhood. *British Medical Journal*, 2(5361):844-846, 1963.

Five cases are reported of imipramine poisoning in young children, and attention is drawn to the increasing importance of this hazard. Available literature and case studies indicate that certain features of imipramine poisoning are reasonably well established. As little as 75 to 100 mg can produce severe symptoms in small children, and as little as 350 mg can prove fatal. The clinical effects are dominated by CNS manifestations and, in more severe instances, by cardiac disturbances with profound abnormalities in the ECG.

Selly Oak Hospital
Birmingham, England

- 1717 Pethidine poisoning. *British Medical Journal*, 2(5361):822, 1963.

Pethidine may be dangerous to patients with liver disease or to those receiving MAO inhibitors, when an alarming state of collapse, confusion, and cerebral excitement may be produced. This usually responds to treatment with chlorpromazine and corticosteroids, but fatalities have occurred. Pethidine is dependent on the enzyme systems in the microsomes in liver cells for its detoxication. Normally it is partially hydrolyzed to meperidinic acid and partially demethylated to norpethidine, which is itself hydrolyzed to normeperidinic acid.

Both these substances are then conjugated in the liver. It is possible to influence the excretion of pethidine and related compounds by altering the pH of the urine. This could have practical importance in the management of patients with pethidine poisoning. After a single oral dose of 50 mg norpethidine or 75 mg ethoheptazine, up to four times as much of the drug is excreted in acid than in alkaline urine. Prompt acidification might help to prevent disaster when poisoning is suspected.

(No address)

- 1718 Sargent, William. **Antidepressant drugs and liver damage.** *British Medical Journal*, 2(5360):806, 1963. (Letter).

Two deaths, rightly or wrongly attributed to liver damage caused by phenoxypropazine, raise the problem of the hepatotoxic effects of the MAO-inhibitor group of drugs. The possible toxic effects of these drugs, and dangers supposed to arise from combining certain groups of them, are emphasized by the cessation of the use of iproniazid in America because of supposed deaths from liver damage and the recent withdrawal in England of phenoxypropazine. Warnings have been issued against combining the MAO inhibitors, like phenelzine, with imipramine and amitriptyline. On the other hand, large amounts of iproniazid have been used in 3,000 to 4,000 patients without dangerous effects, and it has been found possible to combine drugs like iproniazid, phenelzine, and isocarboxazid with amitriptyline and imipramine in hundreds of patients provided that reasonable precautions against postural hypotensive symptoms are taken by adjusting dosages.

St. Thomas's Hospital
London, S.E.1, England

- 1719 Little, J. Crawford. A case of primary addiction to meprobamate. *British Medical Journal*, 2(5360):794, 1963.

Addiction to meprobamate is reported in a 29-year-old woman being treated for neurosis. The patient was treated first

with chlordiazepoxide and then with trifluoperazine, neither of which was successful. Meprobamate (400 mg b.i.d.) caused greater response and reduced her anxiety. Two years later, after a gradual increase of the dosage to 6 tablets on rising and 5 more during the day, she experienced intolerable depression and irritation upon any lessening or withdrawal of the drug. Within a month, she increased her dosage to 16 400-mg tablets a day (6.4 g/day), her speech was slurred, and her movements were slow and ataxic. Attempts to switch to chlordiazepoxide, imipramine, and, finally, phenelzine had to be abandoned because of side effects. In a treatment program set up to cure her addiction, she was initially given four 400-mg meprobamate tablets and 100 mg chlorpromazine daily. Meprobamate was gradually withdrawn, during which time she exhibited motor restlessness and quite severe anxiety requiring considerable reassurance and support. She was finally discharged on 400 mg chlorpromazine daily.

St. James's Hospital
London, England

1720 O'Sullivan, Donal. **Foetal death after pethidine and promazine.**
British Medical Journal, 2(5359):748-749, 1963. (Letter).

comment is made on a report of fetal death due to the combined use of pethidine and promazine. Other factors reported in the case could have caused or contributed to the asphyxiation of the fetus. The general anesthetic given for the caesarean section included halothane, which is known to have depressant effects. The dyskinetic labor was accompanied by hypertension and proteinuria, all of which could have contributed to the fetal death.

Staring Cross Hospital
London, W.C.2, England

1721 Lomas, H. B. **Cyclizine Hydrochloride.**
British Medical Journal, 2(5354):444, 1963. (Letter).

There is no evidence that cyclizine HCl is teratogenic in man and a great deal of

evidence to show that it is not. Abnormalities can be induced in a small percentage of the offspring of laboratory animals when the drug is given in enormous dosage. Although cyclizine HCl is an effective anti-nauseant, it should not be taken by any pregnant woman except upon the advice of her doctor.

The Wellcome Foundation Ltd.
London, N.W.1, England

1722 Millen, Hugh. **Advertisement of "Marzine" (cyclizine hydrochloride).**
British Medical Journal, 2(5350):183, 1963. (Letter).

A ship's surgeon asks how he can comply with the manufacturer's warning against the use of cyclizine HCl, which may possess teratogenic side effects, in pregnant patients when the drug is openly advertised without warnings and is available as a seasickness remedy without prescription.

R.M.S. Rangitane

1723 Amias, A. G. & Fairbairn, D. **Foetal death after pethidine and promazine.**
British Medical Journal, 2(5354):432-433, 1963.

Promazine with pethidine has been used intramuscularly (one or more injections of 50 mg promazine with 150 mg pethidine as sedation in labor without ill effects to mother or child. An intravenous mixture of pethidine, promazine, and levallorphan has also been used before performing delivery under pudendal block. Chlorpromazine was the first of the phenothiazines to have been used in obstetrics but was found to be too unpredictable and to cause significant hypotension. Pethidine--promazine mixtures were found to be safer and with no, or minimal, side effects. However, one case, recorded here, resulted in temporary maternal collapse and the death of the baby 40 hours after delivery. It seems clear that an unexpectedly high potentiation of pethidine by any of the phenothiazines may occasionally take place even after a carefully controlled injection.

St. George's Hospital
London, England

SIDE EFFECTS 1724-1728

- 1724 Smith, R. C. Nimmo & Grieve, R. C.
Peripheral neuropathy after amitriptyline. British Medical Journal, 2(5351): 254, 1963. (Letter).

Peripheral neuropathy in a 20-year-old single woman is reported as a possible side effect of amitriptyline therapy. The patient, diagnosed as feeble-minded with associated schizophrenic psychosis, was prescribed 25 mg amitriptyline t.i.d. for tension and headaches. Four months after initiation of amitriptyline therapy, the patient complained of weakness and numbness of her legs; amitriptyline was discontinued. Two weeks later, tendon reflexes in the legs were found to be absent, and the patient was also complaining of paresthesia and numbness of her fingers. After physical examination, it was concluded that she was recovering from a toxic peripheral neuropathy, possibly induced amitriptyline; the patient was receiving no other drug at the time of onset of symptoms.

Stranraer Health Centre
Stranraer, Wigtownshire, England

- 1725 Conlon, Michael F. **Addiction to chlorodyne.** British Medical Journal, 2(5366):1177-1178, 1963.

The case histories of three patients (2 males, 1 female) addicted to chlorodyne are reported. The patients (41 to 53 years of age) experienced serious mental and physical deterioration, including peripheral neuropathy. The average daily consumption was 170 ml chlorodyne---morphine (0.4 g) and chloroform (21 ml). Two patients had low blood pressure and liver damage, and all three had behavior disturbances. The ready availability and the large quantities of morphine and chloroform consumed made chlorodyne a dangerous drug. It is suggested that chlorodyne be considered as a poison, available only on prescription.

All Saints' Hospital and Uffculme Clinic
Birmingham, England

- 1726 Kuenssberg, E. V. **Diethylpropion and addiction.** British Medical Journal, 2(5369):1406, 1963. (Letter).

Single tablets of amphetamine and of diethylpropion hydrochloride are available

easily though at high cost. The willingness to pay this cost suggests addiction, and a warning that these drugs can lead from habituation to addiction is long overdue.

Edinburgh, Scotland

- 1727 Thomas, J. C. Sawle. **Monoamine-oxidase inhibitors and cheese.** British Medical Journal, 2(5369):1046, 1963. (Letter).

A case of severe headache is reported in a 26-year-old man receiving phenelzine (15 mg t.i.d.) and chlordiazepoxide (5 mg t.i.d.) for depression. The severe headaches were found to occur after the ingestion of cheese. All patients on any form of MAO inhibitor should be told to avoid eating cheese while under treatment.

London, W.1, England

- 1728 Kumar, K. **Addiction to chlorodyne.** British Medical Journal, 2(5369): 1411, 1963. (Letter).

The author comments on an article (November 9 issue) reporting the case history of a 61-year-old, married housewife who became addicted to alcohol and chlorodyne for 5 years. At first, she used alcohol only to relieve her "low spirits" and "loneliness", but later she began taking chlorodyne quite frequently with alcohol to relieve her symptoms. She has been hospitalized on four occasions. Examination on her first admission showed all systems normal except for pigmentation of the buccal mucous membrane with angular stomatitis. She was slightly disoriented in time and place with slight impairment of recent memory, and her mood was apathetic and depressed. Initially she was treated with injections of a Vitamin B complex and ascorbic acid preparation and chlorpromazine, followed by amitriptyline and chlordiazepoxide for depression. In a few weeks, she became symptom-free. She was subsequently hospitalized on three more occasions, twice for chlorodyne overdose and once for barbiturate overdose. Although her acute problem was alcoholism and chlorodyne addiction, the underlying cause appeared to

the depression. The author concurs with the previous suggestion that chlorodyne should be available only on prescription.

The Towers Hospital
Leicester, England

729 Snell, W. E. **Addiction to chlorodyne.** British Medical Journal, 2(5369): 411, 1963. (Letter).

A case of addiction to chlorodyne in a 63-year-old woman is reported. Other cases of suspected addiction to chlorodyne are cited, and it is suggested that chlorodyne be available only on prescription.

Polindale Hospital
London, NW.9, England

730 Myers, W. H. & Law, Evelyn. **Addiction to amphetamine.** British Medical Journal, 2(5371):1536, 1963. (Letter).

The problem of demands by patients for amphetamines in general medical practice is discussed. The following measures are suggested for curtailing these demands: (1) suggesting that these compounds may cause lack of potency and have been known to cause blindness by cataract; (2) breaking down the tablet into its ingredients and prescribing these separately with a decreasing dose of amphetamine; and (3) substituting a brief period of treatment with an antidepressant, such as phenelzine, in those patients in whom it is justifiable.

London, SE.9, England

731 Donaldson, Ian A. **Collapse after pethidine and promazine.** British Medical Journal, 2(5372):1592, 1963. (Letter).

A case is reported of collapse due to i.m. injection of pethidine and promazine. A 30-year-old primigravida, in the thirty-ninth week of pregnancy, had a blood-pressure of 140/90. She was admitted at term with a blood pressure of 150/70. Pethidine

(100 mg) with promazine (50 mg) was given i.m. prior to vaginal examination. Shortly afterwards, she collapsed and became cyanotic; the limbs were spastic and the pulse imperceptible. Oxygen was administered, and coramine (2.5 ml) and aminophylline (10 ml) were given i.v. She was tilted head down, and then she slowly recovered. After artificial rupture of the membranes, spontaneous normal delivery occurred. Her blood pressure rose during the same stages of her second pregnancy; pethidine and promazine were not administered. She went into spontaneous labor in the forty-second week of her second pregnancy and delivered normally.

London W.1, England

1732 Davies, D. M. & Allaye, Richard. **Amitriptyline poisoning.** Lancet, 2(7307):543, 1963.

The clinical features of two cases of amitriptyline poisoning are reported. In the first case, a 67-year-old man ingested 1,000 mg amitriptyline. Pertinent features of the clinical course during the period of unconsciousness were: very slow deep respirations, raised blood pressure, only slight reduction of body temperature, preservation of deep reflexes, extensor plantar responses, and the lack of response to light of the normal-sized pupils. After recovery from coma, there was confusion, tremulousness, and agitation. In the second case, a 70-year-old woman ingested 950 mg amitriptyline, and died 4 hours after admission to the hospital. The clinical features were: deep respiration but not unduly slow; reduced blood pressure but not greatly so; presence of moderate tachycardia; significant reduction of body temperature; sluggish response to light of normal-sized pupils; and diminution of muscular tone and tendon reflexes. Amitriptyline resembles, in some of its actions, both imipramine and chlorpromazine. Severe overdosage of amitriptyline may result in coma, convulsions, severe hypotension, and urinary retention.

Shotley Bridge General Hospital
Durham, England

SIDE EFFECTS 1733-1736

1733 Oswald, Ian & Thacore, V. R. Amphetamine and phenmetrazine addiction. Physiological abnormalities in the abstinence syndrome. *British Medical Journal*, 2(5354):427-431, 1963.

Evidence is presented to support the view that amphetamine and phenmetrazine preparations are truly addictive, leading to physiological dependence. Six addicts were studied in whom easily measurable neurophysiological abnormalities appeared upon drug withdrawal; case histories for each patient are given. These abnormalities affected the proportion of nocturnal sleep spent in so-called "hind-brain sleep" (with a characteristic EEG, rapid eye movements, and muscle-tension changes). In the abstinence syndrome, this kind of sleep began as soon as 4 minutes (normal about 70 minutes) after onset of sleep, occupied up to 70 minutes in the first 2 hours of sleep, and up to 48% (normal about 22%) of a whole night. Return to normal function took place immediately if the drugs were restored, but, if withheld, return to normal took 3 to 8 weeks.

University of Edinburgh
Edinburgh, Scotland

1734 Ureles, Alvin L. & Rob, Charles, Acute ischemia of a limb complicating methysergide maleate therapy. *Journal of the American Medical Association*, 183(12):1041-1042, 1963.

A case history is reported of a 36-year-old man who was taking 2 mg of methysergide maleate t.i.d. for vasodilating headaches. A month after beginning the methysergide maleate therapy, he developed acute ischemia of his left lower limb, and medication was stopped. For the next 2 weeks, he experienced severe headaches and was administered 100 mg of meperidine hydrochloride. His claudication gradually diminished over a 7-day period. It is observed that large doses of methysergide maleate given to patients with known vascular disease of coronary and peripheral vessels are well tolerated, but the occurrence of ischemic pain in a few patients with known arterial disease requires caution.

260 Crittenden Boulevard
Rochester 20, New York

1735 Orton, Robert. Combining the anti-depressant drugs. *Lancet* 2(7318):1164, 1963. (Letter).

An excellent therapeutic response from a group of patients to a combination of imipramine (4 to 6 tablets daily) and phenelzine (1 to 3 tablets daily) is recorded. The use of drugs in combination requires care and skill, but it can be the means of reversing a serious depressive disorder when all else has failed.

Royal Victoria Infirmary
Newcastle, England

1736 Crause, J. Jaundice associated with haloperidol. *Lancet*, 2(7313):890-891, 1963. (Letter).

A case of jaundice associated with haloperidol is reported. A 71-year-old man admitted to the hospital for a manic illness was found to have signs of chronic bronchitis and emphysema. Treatment was instituted with oxytetracycline 250 mg every 6 hours. Three days later, treatment with haloperidol 1.5 mg t.i.d. was begun and the dose increased to 1.5 mg q.i.d. 5 days later. Digoxin (0.25 mg) was given every 4 hours the day after the increased dose of haloperidol was given, and the dose of oxytetracycline was increased to 500 mg every 6 hours. Three days later, the patient was considerably improved, but he complained of nausea and began to vomit once or twice a day. Penicillin was substituted for oxytetracycline. Four days later the patient was seen to be jaundiced. The urine was dark and the feces were light in color. Digoxin and haloperidol were discontinued. The absence of physical signs in the pre-icteric period suggests the jaundice was more likely due to a drug, and the patient's low-normal white cell count without relative lymphocytosis supports this contention. In a few cases, digoxin has been implicated in jaundice; oxytetracycline has caused it but only when given in very high doses and intravenously. It seems probable that in this case haloperidol was responsible for the development of an allergic jaundice.

Coney Hill Hospital
Gloucester, England

1737 Oakley, D. P. & Lauth, H. Haloperidol and anticoagulant treatment. *Lancet*, 2(7319):1231, 1963. (Letter).

A 45-year-old man who had two attacks of coronary thrombosis (March and April 1963) was subsequently maintained with phenindione (50 mg daily). Following a short depressive illness (September 1963), after which he had an abrupt swing of mood into hypomania, he was admitted to the hospital and injections of 5 mg haloperidol were given eight-hourly for 24 hours followed by 3 mg orally b.i.d. Phenindione was continued and daily blood samples were submitted for thrombotest. There was difficulty obtaining optimal coagulation value. Phenindione was increased to 100 mg at night and 50 mg in the morning with little effect on coagulation. Haloperidol was reduced to 1.5 mg b.i.d. and phenindione to 100 mg daily. Eventually haloperidol was discontinued and optimal coagulation value was obtained and maintained with 50 mg phenindione daily.

Stanley Royd Hospital
Wakefield, England

1738 Rees, Linford & Pare, C. M. B. Toxic effects of monoamine-oxidase inhibitors. *Lancet*, 2(7320):1279-1280, 1963. (Letter).

Phenoxypipazine has been withdrawn from the English market and iproniazid from the American market because of publicity given the occasional fatality associated with the antidepressant drugs of the MAO inhibitor type. While it is useful to consider this type together as a class in relation to certain therapeutic possibilities, each drug has its individual characteristics, particularly in relation to side effects and toxicity. In addition to the striking dissimilarity between iproniazid and newer MAO inhibitors in the incidence of jaundice, some drugs are nonspecific and will therefore potentiate pethidine; others (for example, isocarboxazid and nialamide) do not potentiate pethidine in animals. Amilcypromine, which has the greatest effect in potentiating the action of catecholamines, differs from the other MAO inhibitors in having a direct sympathomimetic action so that there may, in fact, be a dual effect in this potentiation.

Bartholomew's Hospital
London, E.C.1, England

1739 Gault, J. E. Agranulocytosis due to amitriptyline. *Lancet*, 2(7297):44-45, 1963.

A case of agranulocytosis due to amitriptyline is reported in a 39-year-old female depressive. When the patient showed signs of dry mouth, drowsiness, and tremulousness, the amitriptyline dosage was reduced from 50 mg five times daily to 25 mg five times daily, to which amiphenazole (20 mg t.i.d.) and chlorpromazine (25 mg t.i.d.) were added. After 3 weeks, amitriptyline was reduced to 25 mg q.i.d. and chlorpromazine and amiphenazole were stopped. With a recurrence of depression and sleeplessness, amitriptyline was again prescribed at a dose of 25 mg t.i.d. Within 16 days, she reported having bleeding gums, sore throat, and pharyngeal ulcers. She was admitted to the hospital and treated with crystalline penicillin 500,000 units 6-hourly and streptomycin 0.5 g b.i.d., barrier nursing, mouth toilets, fluid feeding, and aspirin for pain. During the next few days she became extremely depressed, but gradually her temperature fell, the mouth returned to normal, and the depression resolved. The blood picture returned to normal shortly afterward.

Bendigo, Victoria, Australia

1740 Death associated with Drazine. *Lancet*, 2(7300):205, 1963.

Autopsy of a 40-year-old woman who had been treated for depression by her own doctor with the MAO inhibitor phenoxypipazine hydrogen maleate revealed massive destruction of liver cells. The opinion of the pathologist was that death was probably caused by the drug rather than by a virus disease. General distribution of the drug will be suspended while it is subjected to critical reassessment by the manufacturer, Smith & Nephew Pharmaceuticals, Ltd.

(No address)

1741 Houghton, A. W. J. Ipecacuanha in barbiturate tablets. *Lancet*, 2(7303):357, 1963. (Letter).

The author reports of the possible use of ipecacuanha in barbiturate tablets to insure against overdoses of this medication. In

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therapeutic doses ipecacuanha has no effect, but in larger doses severe nausea is induced, while in dangerous amounts immediate vomiting occurs. The larger the overdose the greater the amount of vomiting. Thus, this presents a novel way of preventing the effects of an overdose of barbiturates.

Royal Salop Infirmary
Shrewsbury, England

- 1742 Sedman, G. Increased libido with chlorprothixene. British Medical Journal, 2(5363):999-1000, 1963. (Letter).

A case is reported of a 37-year-old married woman, suffering from manic-depressive psychosis, who developed increased libido following the administration of chlorprothixene. The patient from the age of 17 has had numerous attacks of depression and mania. Chlorprothixene, 50 mg t.i.d., was prescribed to be taken during the manic phase. A few days after taking the drug, she noted a marked increase in libido, which she could only relieve by masturbation. She stopped taking the tablets and the effect dwindled within a day or two. Her manic phases were partially controlled by prothipendyl HCl 40 mg t.i.d. After receiving chlorprothixene a year later, 30 mg t.i.d., the libido increased and she again resorted to masturbation. The effect dwindled rapidly once she stopped taking the drug, hence one must conclude that it was an effect of the drug.

University of Manchester
Manchester, England

- 1743 Another death associated with Drazine. Lancet, 2(7304):419, 1963.

A death associated with phenoxypropazine hydrogen maleate medication is reported. The patient, a 46-year-old female, had been given phenoxypropazine 5 mg t.i.d. for treatment of depression. When seen by the doctor, nausea, postural dizziness, and tinnitus had prevented her taking the drug for 3 or 4 days. Upon examination, she was found to have a furred tongue and a suspicion of icterus of the conjunctivae. Two days later jaundice was clinically obvious; the patient had mild pruritus and

putty-colored stools. When admitted to the hospital, the confusion and flapping tremor increased and was rapidly succeeded by coma. At necropsy, the liver was completely necrotic save for two small nodules of regeneration.

(No address)

- 1744 Rail, J. F. W. Ipecacuanha in barbiturate tablets. Lancet, 2(7305):461, 1963. (Letter).

In a comment on an article that suggested that the emetic ipecacuanha be added to barbiturates to prevent overdosage, a mixture of amylobarbitol and its specific antagonist megitimide is suggested as being safer.

London SW.17, England

- 1745 Nymark, M. & Nielsen, I. Møller. Reactions due to the combination of monoamineoxidase inhibitors with thymoleptics, pethidine, or methylamphetamine. Lancet, 2(7306):524-525, 1963. (Letter).

Severe and even fatal reactions may follow when imipramine is given within about 14 days after administration of MAO inhibitors. Amitriptyline could be assumed to provoke the same severe reactions, although only one case with mild reaction is reported in the literature. Pethidine or methylamphetamine administered to patients who have been taking MAO inhibitors can provoke serious side effects. When pretreated with phenelzine, a fivefold reduction was found in the average lethal dose of amphetamine, methylamphetamine, and pethidine in mice. Male rabbits were pretreated with intramuscular injections of β -p-chlorophenylmercaptoethyl hydrazine for 3 days and an intravenous injection 1 hour before administration of either amitriptyline (5 mg/kg) or pethidine 5, 10, or 20 mg/kg. Thirteen developed hyperthermia and died 1 hour to 2-1/2 hours after amitriptyline injection. Of the pethidine group, 4 became hyperpyrexial and died within an hour after injection. Despite some variations, there is a striking similarity to the picture in man. The thymoleptics are known to potentiate noradrenaline, which is concentrated

in the hypothalamic region of the diencephalon in the brainstem. The neuroleptics chlorpromazine and chlorprothixene act on the diencephalon and reverse the hypomoleptic action.

Lundbeck and Co. A/S
Copenhagen-Valby, Denmark

746 Pare, C. M. B. Potentiation of monoamine-oxidase inhibitors by tryptophan. *Lancet*, 2(7306):527-528, 1963. (Letter).

In 14 patients tryptophan was combined with various MAO inhibitors (isocarboxazid, phenelzine, nialimide, Actomol, Parstelin). In 10 patients, it was given with imipramine or amitriptyline. Of the 14 patients, 6 showed striking improvement within 2 or 3 days of the tryptophan being added. Only one patient of those in whom tryptophan was combined with either imipramine or amitriptyline showed a significant improvement; the other showed no response at all. Only one had noteworthy side effects (nausea and malaise). The side effects were pronounced and much more frequent in the patients in whom tryptophan was given with MAO inhibitors. These findings demonstrate a potentiation of the antidepressant effect of MAO inhibitors by tryptophan. It is suggested since tryptophan is of little benefit when combined with imipramine or amitriptyline it does not act as a nonspecific euphoriant but specifically increases the brain concentrations of one of its metabolites in action with an amine oxidase inhibitor. Taken in conjunction with the negative findings with TP, DOPA, and phenylalanine, it is suggested that the antidepressant effect of amine-oxidase inhibitors may be brought about by the increase of one of the non-hydroxylated derivatives of tryptophan rather than an hydroxylated form or one of the catecholamines.

Bartholomew's Hospital
London, E.C.1, England

747 Clemmesen, Carl. Ipecacuanha in barbiturate tablets. *Lancet*, 2(7307):581, 1963. (Letter).

Incorporating a little ipecacuanha in each barbiturate tablet to produce vomiting after overdose has not proved successful.

The tablets became less solid and the barbiturates dominated the ipecacuanha to the extent that no vomiting occurred at all.

Bispebjerg Hospital
Copenhagen, Denmark

1748 Nicholson, W. A. Ipecacuanha in barbiturate tablets. *Lancet*, 2(7307):580-581, 1963. (Letter).

The problem of barbiturate overdosage and addiction and attempted suicide by overdosage of barbiturates, aspirin, codeine, and tranquilizers is discussed. The easy availability of these drugs, and the fact that patients may not always see or consult the same physician, and that people take drugs that are not prescribed for them all contribute to the difficulty in controlling potentially habit-forming or dangerous drugs.

General Hospital
West Hartlepool, Durham, England

1749 Reah, T. G. Ipecacuanha in barbiturate tablets. *Lancet*, 2(7305):461-462, 1963. (Letter).

The answer to the question of how to prevent overdosage of barbiturates and tranquilizers is not as simple as adding ipecacuanha to each barbiturate tablet. Patients should be weaned from their addiction to barbiturates. The barbiturates and tranquilizers should not be so freely prescribed by practitioners.

Harrogate, England

1750 Smithells, R. W. & Chinn, E. R. Meclozine and foetal abnormalities. *British Medical Journal*, 1(5346):1678-1679, 1963. (Letter).

Records of 237 infants born after 28 weeks' gestation to mothers for whom meclizine was prescribed during the first 12 weeks of pregnancy showed only three cases of malformation: one with anencephaly; one with subglottic stenosis; and one with choanal stenosis. The preparation that had been

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given the mothers was ancologin, which is a combination of meclizine and pyridoxine. The occurrence of three abnormal fetuses among 257 infants does not differ significantly from the expected incidence (2% to 3%).

University of Liverpool
Liverpool, England

- 1751 Rab, S. M. **Two cases of chloroquine psychosis.** British Medical Journal, 1(5340):1275, 1963.

Two cases of toxic psychosis due to chloroquine are reported. The two male patients, aged 24 and 34 years, were given chloroquine sulfate, 250 mg q.i.d., for treatment of amoebic hepatitis. After treatment for 6 days, both patients were confused, irrational, and agitated. A diagnosis of toxic psychosis was made in both cases, and the drug was stopped. The two patients were treated for their psychosis with chlorpromazine, which caused a dramatic recovery. The absence of any past history of mental ailment in both patients and the lack of any clinical features of hepatocellular failure make these cases of toxic psychosis due to chloroquine.

Mitford Medical College
Dacca, Pakistan

- 1752 Pettinger, William A., Horwitz, David, & Sjoerdsma, Albert. **Lactation due to methyldopa.** British Medical Journal, 1(5343):1460, 1963.

Lactation was observed in 5 of 15 women under treatment with methyldopa for hypertension. The patients were 33 to 47 years old, and one was postmenopausal. The doses administered were 2.0 to 3.75 g/day, and the duration of treatment ranged from 7 to 14 months. In two subjects, lactation ceased within 3 weeks after methyldopa was discontinued. In another patient, lactation stopped when treatment was switched to guanethidine, but returned with resumption of methyldopa. Amenorrhea and breast changes in the latter patient corresponded to these changes in medication. Methyldopa has sympatholytic activity and readily enters the CNS, as do reserpine and various tranquilizing agents known to cause non-puerperal lactation.

National Heart Institute
Bethesda, Maryland

- 1753 Burry, A. F. **Meclozine and foetal abnormalities.** British Medical Journal, 1(5343):1476, 1963. (Letter).

The occurrence of congenital diaphragmatic hernia in consecutive siblings is linked with the fact that the mother had been treated with meclizine in both pregnancies. Two later pregnancies, in which meclizine was not prescribed, resulted in the birth of normal infants to this mother.

Princess Alexandra Hospital
Brisbane, Queensland, Australia

- 1754 Gander, Derek R. & Devlin, H. Brendan. **Ileus after amitriptyline.** British Medical Journal, 1(5338):1160, 1963. (Letter).

A case of severe constipation associated with amitriptyline is reported. A 54-year-old woman was admitted to the hospital with pustular psoriasis; this was treated with "synalar" cream. Depressive symptoms were noted, and, on psychiatric advice, amitriptyline 25 mg t.i.d. was prescribed. The dose was increased 14 days later to 50 mg t.i.d. In less than 3 weeks, she became severely constipated, and, within 2 days thereafter, there was passage of neither flatus nor feces. Laparotomy was performed a week later. The ileum was found distended and the terminal 18 inches filled with formed fecal material. Postoperatively, she was managed with naso-gastric suction and intravenous fluids. Three days later, her abdomen was reopened and a left iliac colostomy performed. The next day, an intravenous pitressin infusion of 5 i.u. in 1 liter was administered in an 8-hour period. No flatus passed, and the dose was doubled. Twenty-four hours later, following a total dose of 25 i.u. of pitressin, her colostomy started to function. Pitressin was discontinued. Conservative measures, such as the administration of prostigmine or pitressin, would not alone have proved successful in relieving this patient's obstruction.

St. Thomas's Hospital
London S.E.1, England

1755 Ayd, Frank J. **Illeus after amitriptyline.** British Medical Journal, 1(5343):1477, 1963. (Letter: comment on letter by Derek R. Gander and H. Brendan Evlin.)

It is not easy to decide whether ileus was due to amitriptyline or to other factors in a previously reported case where the patient had been treated with the drug for another ailment. It is essential that medical journals publish quickly reports of serious side effects of pharmaceuticals, and the authors of these reports should include sufficiently detailed information to enable valid conclusions to be reached.

me, Italy

1756 McBride, W. **Cyclizine and congenital abnormalities.** British Medical Journal, 1(5338):1157-1158, 1963. (Letter).

A study of babies born with congenital abnormalities in the years 1957 to 1962 at the Women's Hospital has shown that there were 24 whose mothers were given cyclizine HCl during pregnancy for morning sickness. Of these 24, congenital heart disease was present in five, cleft palate in five, myeloencephalocele in two, hydrocephalus in one, anencephaly in one, and lateral congenital cataract in one. Chromosomal anomalies were present in the remaining nine babies. Tests of cyclizine (5 mg/kg) in rabbits indicated that the prevailing anomalies were anophthalmia, microphthalmia, and cataract. These tests, however, were run at dosages 50 times higher than those used in humans. Extrapolation of the animal data to humans at such high dosage is not valid.

dney, N.S.W., Australia

1757 Sniper, Woolfred. **Dangers of monoamine oxidase inhibitors.** British Medical Journal, 1(5337):1088, 1963. (Letter).

Phenelzine and pargiline are added to a previously published list (December 8, 1962 and December 29, 1962 issues) of MAO inhibitors that may produce adverse effects when used in common with other drugs.

Abhill General Hospital
Glasgow, Scotland

1758 **Today's drugs. Danger corner.** British Medical Journal, 1(5326):318, 1963.

Three cases of severe side effects due to drug administration are reported. Two of the cases were asthmatic pregnant women receiving ephedrine, phenobarbital, theophylline, and potassium iodide. In each case, a goitrous child was born, and died soon after birth. A case of acute severe occipital headache was reported after administration of a mixture of tranlylcypromine and trifluoperazine (parstelin).

(No address)

1759 Smirk, Horace. **Hypotensive action of methyldopa.** British Medical Journal, 1(5324):146-151, 1963.

A study of 53 patients was made to determine the hypotensive action and side effects of methyldopa. The effects on blood pressure were evaluated in the individual patients by all-day tests in which the blood pressure was measured hourly. Placebo tablets were also used. In each of 19 patients (12 females, 7 males) who were not receiving any adjuvant drugs, methyldopa was administered in doses that were adjusted to produce a fall in blood pressure to a near normal level. The least daily dose given was 150 mg, the highest 2,000 mg, and the mean 1,403 mg. In 8 patients placebos were given and the blood pressure falls (standing) on methyldopa exceeded the falls on administration of the placebo. Of the 53 patients receiving methyldopa 44 were questioned in detail about side effects. Side effects present included drowsiness, nausea, and mild headache. The most interesting side effects encountered were psychiatric manifestations and disturbance of sleep rhythm. A followup observation of 10 cases, (5 males, 5 females, 41 to 76 years of age) showed that psychiatric manifestations and disturbances of sleep rhythm were of major concern. The degree of postural fall in blood pressure was usually less with methyldopa than with hexamethonium or guanethidine, but the extent to which postural hypotension was exhibited varied with the individual patient and with the drug used.

University of Otago
Dunedin, New Zealand

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- 1760 David, A. & Goodspeed, A. H. "Ancoloxin" and foetal abnormalities. British Medical Journal, 1(5323):121, 1963. (Letter).

Ten cases of fetal abnormality are reviewed in an investigation of any correlation between the date of administration of ancoloxin and the embryological stage at which the deformity must have occurred. In four cases with defects of the spina bifida type, the neural tube was already defective before ancoloxin was given. In one case of rudimentary thumb, administration of ancoloxin was begun after the material date for this type of deformity. In three cases, no material dates in pregnancy are applicable. In one case of imperforate anus, ancoloxin was given during the maternal time. However, there is no indication of an increase in incidence of this malformation during the seven years that ancoloxin has been in use. The occurrence of ancoloxin administration and fetal abnormality in the same pregnancy is therefore purely coincidental, especially in view of the fact of the widespread use of this drug in early pregnancy by an estimated ten million women throughout the world.

The British Drug Houses, Ltd.
London, England

- 1761 Kirman, Brian H. "Ancoloxin" and foetal abnormalities. British Medical Journal, 1(5325):165-166, 1963. (Letter: comment on letter by A. David & A. H. Goodspeed).

Comment is made on a letter (January 12 issue) by Drs. David and Goodspeed which stated that ancoloxin (mecizine and pyridoxine) given at 7-1/2 to 10 weeks after the last menstrual period (LMP) cannot cause meningocele in the embryo. This opinion does not take into account that, since the time of ovulation may vary even in the same woman, fertilization may take place at any time. If it occurs immediately before the date when the next menstrual period is due, at 8 weeks after the LMP, the embryo will only be 4 weeks old and still susceptible to meningocele complication.

Carshalton, Surrey, England

- 1762 James, J. R. "Ancoloxin" and foetal abnormalities. British Medical Journal, 1(5322):59, 1963. (Letter).

This letter questions the usefulness of the facts about ancoloxin (mecizine and pyridoxine) that were published by the College of General Practitioners. Concerning the 784 cases discussed in the publication, necessary data are not included, such as (1) how many abnormalities there were in the 660 cases where no antiemetic was taken; (2) how many of the 124 took ancoloxin; and (3) what was the nature of the three malformations. Without this information, it is impossible to draw conclusions about ancoloxin.

Southsea, England

- 1763 Gallagher, C. "Ancoloxin" and foetal abnormalities. British Medical Journal, 2(5323):121-122, 1963. (Letter: comment on letter by L. A. Ruben.)

A previous article (December 3 issue), which reported 10 cases of unrelated congenital abnormalities said to be due to administration of ancoloxin (mecizine and pyridoxine) in early pregnancy, is condemned for its flimsy evidence.

Liverpool 19, England

- 1764 Campbell, G. D. Chlorpropamide and foetal damage. British Medical Journal, 1(5322):59, 1963. (Letter).

In 19 pregnancies in diabetic mothers whose diabetes was controlled with 500 mg of chlorpropamide daily, only five fetuses survived. The progress of the five infants was carefully followed. One mother did not return for the followup until 10 months after delivery. Examination of the child at that time showed that it was suffering from an advanced degree of microcephaly, and that it had a spastic quadriplegia. In view of the experiences with this patient, it is felt that there is a strong case for regarding these abnormalities as a result of chlorpropamide therapy. This case makes it more certain that it is correct to withhold chlorpropamide from pregnant, insulin-independent diabetics in favor of tolbutamide.

King Edward VIII Hospital
Durban, Natal, South Africa

1765 Miller, Ronald B. **Tranlycypromine and cheese.** British Medical Journal, (1963):1593, 1963. (Letter).

A case is reported of an adverse reaction following the eating of cheese in a 46-year-old woman taking tranlycypromine. After a meal of cheese, she developed a severe headache which spread to the frontal region. She was nauseated and vomited. She had blurred vision that receded to complete blindness, and she went into a generalized epileptiform convulsion, lasting minutes, which was treated with phenobarbital i.m. (0.2 g). Upon hospitalization she was given paraldehyde, and her condition was normal after awakening the next morning.

Willesden, Kent, England

1766 Vorster, De. W. **Tranquillisers in pregnancy.** Lancet, 2(7308):635-636, 1963. (Letter).

The rare published cases of fetal abnormality possibly attributed to the use of certain psychotropic drugs, apart from thalidomide, may be accounted for by genetic variations in drug response. Considering the effect on the emotional development of the offspring of rats fed chlorpromazine, meprobamate, and other such drugs during pregnancies, it might be possible to prevent certain psychoses in such offspring by administration of an antipsychotic drug to the mother during pregnancy.

Stellenbosch
Union of South Africa

1767 Davies, D. M. & Allaye, Richard. **Amitriptyline poisoning.** Lancet, (1963):643, 1963.

A case of acute amitriptyline poisoning is reported in a 16-year-old girl who ingested 1,250 mg of the drug 3-1/2 hours before admission to hospital. The important clinical features were coma, deep respirations of normal rate, tachycardia, subnormal temperature, raised blood pressure, increase in muscle tone and deep tendon reflexes, and normal plantar responses. Gastric lavage

was performed, but no other treatment was given. Because this case resembled two previous cases, a correct diagnosis was made before specimens of the tablets taken were identified.

Shotley Bridge General Hospital
Durham, England

1768 Mellin, Gilbert W. & Katzenstein, Michael. **Meclozine and foetal abnormalities.** Lancet, 1(7274):222-223, 1963. (Letter).

The results of a study of 3,200 pregnancies are presented to ascertain if meclizine contributes to fetal abnormalities. From the 266 pregnancies resulting in malformed infants, tables are presented, indicating the cases in which meclizine, dimenhydrinate, and cyclizine were taken. Also tabulated are the dosages of meclizine ingested and the outcome of pregnancies of other control groups.

College of Physicians and Surgeons
of Columbia University
New York, New York

1769 Dornhorst, A. C. & Robinson, B. F. **Chloroquine psychosis?** Lancet, 1(7272):108, 1963. (Letter).

The case history is presented of a 65-year-old woman with rheumatoid arthritis, who experienced toxic psychosis that may have been caused by chloroquine therapy. After admission to hospital, the patient was administered chloroquine sulfate (600 mg daily). On the fourth day of treatment, she became agitated and confused, and chloroquine was discontinued. During the fourth week of illness, the patient's mental state improved, and by the end of the eighth week, it was normal. The evidence that psychosis was due to chloroquine therapy is inconclusive, but it is possible that this drug was the cause.

St. George's Hospital Medical School
London SW.1, England

SIDE EFFECTS 1770-1775

- 1770 Hare, E. H. **Potentiation of the antidepressive effect of a monoamine-oxidase inhibitor by tryptophan.** *Lancet*, 1(7275):268-269, 1965. (Letter).

The author comments on two possible sources of error in a clinical trial concerning the potentiation of the antidepressive effect of an MAO inhibitor by tryptophan. Since patients on tryptophan exhibited side effects and control patients did not, it appears that the psychiatrist who made the clinical evaluations may have been biased. The second error stems from the adding together of the ratings of 21 different symptoms.

Bethlem Royal Hospital
Beckenham, Kent, England

- 1771 Bradley, J. J. & Francis, J. G. **Reactions to pethidine or opium derivatives in patients receiving monoamine-oxidase inhibitors.** *Lancet*, 1(7277):386, 1963. (Letter).

Information is required concerning whether the incidence and mechanism of undesirable reactions in patients treated simultaneously with MAO inhibitors and pethidine or opium derivatives is a common complication or a rare idiosyncrasy.

St. Thomas' Hospital
London, SE.1, England

- 1772 Hamilton, Max. **Potentiation of the antidepressant effect of a monoamineoxidase inhibitor by tryptophan.** *Lancet*, 1(7277):384-385, 1963. (Letter).

The author gives his opinion of the investigation and subsequent critical comment concerning a previous criticism (February 2 issue) of a clinical trial of the potentiation of antidepressive effect of an MAO inhibitor by tryptophan (January 12 issue). The fact that the double blind in the trial was broken by the evidence of side reaction in the tryptophan group, but not in the control group, is not very important, since any investigation that introduces a control series must be regarded as a great advance. The second point of criticism raised concerned the theoretical approach involved in using rating scales. The author expresses the idea that, even with its defects, this investigation represents a remarkable

advance and that this work should be repeated and developed with every possible precaution.

University of Leeds
Leeds, Yorkshire, England

- 1773 Norris, T. St. M. **Promethazine and drug-induced jaundice.** *Lancet*, 1(7277):394, 1963. (Letter).

The case of the death of a 42-year-old woman who had become jaundiced while taking chlorpromazine (25 mg b.i.d.) is described. The drug was discontinued, and promethazine HCl (25 mg b.i.d.) was prescribed. Death was attributed to a combination of jaundice and agranulocytosis. It is concluded that promethazine HCl should not be prescribed in patients suffering from drug-sensitivity jaundice.

Whittington Hospital
London, N.19, England

- 1774 Robson, J. M. & Sullivan, F. M. **The production of foetal abnormalities in rabbits by imipramine.** *Lancet*, 1(7282):638-639, 1963.

The production of fetal abnormalities by imipramine was studied in 12 pregnant rabbits of various strains. The average dose was about 15 mg/kg s.c., daily (range, 5 to 30 mg/kg). The first dose was given 1 hour after mating and was continued for 13 days (1 rabbit), 17 days (6 rabbits), or 20 days (5 rabbits). Seven fetuses were affected in some way, and in three fetuses gross abnormalities of the limbs and cranium were observed. On the basis of the results, it is suggested that imipramine should be used with caution in women during pregnancy and that evidence should be obtained as to whether imipramine has produced human fetal abnormalities.

Guy's Hospital Medical School
London SE.1, England

- 1775 Brownlee, George & Williams, G. W. **Potentiation of amphetamine and pethidine by monoamineoxidase inhibitors.** *Lancet*, 1(7282):669, 1963. (Letter).

The toxic effects of amphetamine, methylamphetamine, and pethidine in mice pretreated with MAO inhibitors have been

described. Male mice (18 to 24 g) were injected i.p. with amphetamine (74 to 95 mg/kg), methylamphetamine (46 to 65 mg/kg), and pethidine (145 ± 7.4 mg/kg). A second group was pretreated with phenelzine (100 mg/kg i.p.) 4 hours before the stimulant drugs. In the presence of the MAO inhibitor, a small dose of the stimulants had an effect of 5 times this amount in normal animals. Amphetamine and methylamphetamine in lethal doses produced central stimulation within 5 minutes, which gave way to respiratory depression. This action was delayed in mice first treated with phenelzine. Cerebrospinal axis intoxication occurred within 5 minutes after pethidine or pethidine plus MAO inhibitors, and deaths occurred within 5 minutes. To form a simple explanation of mechanism of action, common to both drugs, it was assumed that an enzyme that usually metabolizes these drugs has been inhibited.

King's College
London, WC.2, England

1776 Wolff, Frederick W., Parmley, William W., White, Kathleen, & Okun, Ronald. Drug-induced diabetes. Diabetogenic activity of long-term administration of benzothiadiazines. Journal of the American Medical Association, 185(7):568-574, 1963.

This study was designed to obtain an overall evaluation of therapy in essential hypertension. Forty-five patients (34 females, 11 males; average weight, 171 pounds; average age, 51 years) were given benzothiadiazines (BZD), and 26 patients (8 females, 8 males; average weight, 163 pounds; average age, 50 years) were not given BZD. The BZD's administered were chlorothiazide (0.5 g b.i.d.) or hydrochlorothiazide (25.0 mg q.i.d.) in addition to reserpine (0.25 mg t.i.d.). The placebo group received tablets identical in appearance to those prescribed for the treatment group. At the beginning of the study, the mean serum urea nitrogen (SUN) for the BZD group was 21 mg/100 cc, and the latest mean SUN of the 8 taking BZD for congestive heart failure was 17 mg/100 cc; for the 37 patients taking BZD as another hypotensive drug, the mean SUN was 21 mg/100 cc. The mean SUN for those given no BZD was 18 mg/100 cc at the beginning and the latest mean SUN was 18 mg/100 cc. There was, therefore, no evidence of any effect of BZD medication on the SUN. The latest supine blood pressure for the BZD group was 154/97 mm Hg and for the control group it was 181/113 mm Hg.

The mean fasting blood sugar of BZD group was 97 mg %; 2 patients developed diabetes. No diabetes developed in patients not given BZD. This diabetogenic activity of BZD suggests that BZD should not be given to young or middle-aged hypertensives in whom there is a lengthy life expectancy and for whom alternate hypotensive therapy is feasible.

The Johns Hopkins University
School of Medicine
Baltimore, Maryland

1777 van Rossum, J. M. Potential danger of monoamineoxidase inhibitors and α -methyldopa. Lancet, 1(7287):950-951, 1963. (Letter).

In mice pretreated with an MAO inhibitor, α -methyldopa elicited a strong and prolonged central excitation. Since L- α -methyldopa is used as an antihypertensive, it may be dangerous to prescribe iproniazid, isocarboxazid, nialamide, pargyline, phenelzine, pheniprazine, pivazine, or tranlycypromine to hypertensive patients who are on a regimen of α -methyldopa.

University of Nijmegen
Nijmegen, Netherlands

1778 Brownlee, George & Williams, G. W. Monoamineoxidase inhibitors. Lancet, 1(7294):1323, 1963. (Letter).

Pethidine experiments which gave a 5-fold potentiation after phenelzine were made with A.R.C. male mice, T0 strain (18 to 24 g). Another pethidine experiment, which gave a 1-1/2 times potentiation after phenelzine, was made with M.R.C. female mice, T0₂ strain (15 to 18 g). In both experiments, the drugs were injected i.p. in 0.2 ml volumes; MAO-inhibitor-treated groups had 100 mg of phenelzine 4 hours before pethidine and the mice were five to a cage in groups of 30 to 50. Whether the discrepancy in the results of MAO potentiation of pethidine is caused by strain differences in mice or by other experimental conditions is not known.

King's College
London W.C.2, England

SIDE EFFECTS 1779-1782

- 1779 Tonks, C. M. & Livingston, D. Monoamineoxidase inhibitors. *Lancet*, 1(7294):1323-1324, 1963. (Letter).

A case is reported of potentiation of the action of a pressor amine combination in a patient taking an MAO inhibitor. One capsule of Durophet (a mixture of dextro-amphetamine and levoamphetamine bonded to an ion-exchange resin) 12.5 mg was administered orally to a physically healthy woman (aged 31) under treatment for a depressive illness. The patient had been on a dose of 15 mg phenelzine q.i.d. for 6 weeks and had responded well. One hour after taking the Durophet capsule she was stricken by headache, felt very weak, and shortly became unconscious. On recovering consciousness, she had severe occipital pain, trembling, excessive sweating, and every time she stood up she collapsed. All drugs were stopped, and the patient recovered gradually over the next 5 days. After 8 days without drugs, phenelzine was restarted in a dosage of 15 mg b.i.d. without untoward effects. In patients taking MAO inhibitors, the use of amphetamine or its derivatives is contraindicated.

Department of Psychiatry
Leeds, England

- 1780 Herting, Robert L. Monoamineoxidase inhibitors. *Lancet*, 1(7294):1324, 1963. (Letter).

A comment is made on a previous report of the adverse effects of combined α -methyldopa and pargyline in mice. Results of the animal study cannot be interpreted directly to predict difficulty with the combined use of these drugs when given in therapeutic doses, since the doses used in the mice were much larger than the human therapeutic dose. Many patients have been treated simultaneously with α -methyldopa and pargyline, since both drugs are indicated for the treatment of hypertension and the increase of hypotensive response. No unusual reactions or toxic effects were encountered from a daily dosage administered simultaneously of pargyline (25 to 87.5 mg) and α -methyldopa (250 to 750 mg) over an 11-week period.

Abbott Laboratories
North Chicago, Illinois

- 1781 Addiction to amphetamines. *British Medical Journal*, 2(5354):379-400, 1963.

Evidence to refute the opinion that amphetamine addiction cannot occur is presented. A new method for detecting physical dependence to amphetamine and phenmetrazine as well as the findings of investigators on the dangers of prescribing amphetamine and similar compounds were reviewed.

(No address)

- 1782 Sinks, Lucius F., Parker, Edward C., & Boulware, James R. Trimethadione nephrosis. *American Journal of the Diseases of Children*, 105:196-198, 1963.

A case is reported of the nephrotic syndrome secondary to the administration of oxazolidine-2,4-dione (trimethadione). The patient, a 6-1/2-year-old Caucasian male, was admitted to the hospital in May 1960 because of uncontrolled petit mal seizures. The patient had been treated with trimethadione since December 1958 at increasing dosage up to 900 mg daily. While in the hospital, he developed a dry, erythematous, patchy, generalized pruritic rash. All anticonvulsants were stopped, and treatment with diphenhydramine was initiated. The interval from July 1960 to November 1960 was marked by an increased frequency of petit mal seizures. In an attempt to control the seizures, trimethadione dosage was increased gradually and reached a level of 1,200 mg daily. On December 14, 1960, the patient was noted to have fever, nausea, vomiting, and generalized malaise. Treatment with tetracycline was instituted, and the patient was diagnosed as having nephrosis due to trimethadione administration. Upon admission, trimethadione was withdrawn, and the patient was given a high-protein, low-salt diet. Prednisone was given at 60 mg daily and reduced to 20 mg daily when reserpine was given to control an increase in blood pressure. It is recommended that all patients on trimethadione have frequent urinalysis. The occurrence of erythrocytes, casts, and protein in their urine should prompt considering discontinuance of the drug.

Children's Hospital
Columbus, Ohio

1783 Sunshine, Philip & Yaffe, Sumner J.
**Amitriptyline poisoning. Clinical
 and pathological findings in a fatal case.**
 American Journal of the Diseases of
 Children, 106:501-506, 1963.

The symptoms and pathological findings in a
 15-month-old female child who died after
 the accidental ingestion of 1,250 mg of
 amitriptyline HCl are reported. After ad-
 mission to hospital, the infant developed
 severe neurological and cardiac abnormali-
 ties, including coma, apnea, hypotension,
 and supraventricular tachycardia. The use
 of amobarbital sodium (35 mg i.m.) for
 anticonvulsant purposes may have contrib-
 uted to the profound respiratory depression.
 Peritoneal dialysis was ineffectual in re-
 moving the amitriptyline from the patient's
 body. During an attempted tracheostomy,
 the patient had several generalized seizures
 and died. The pathological findings are
 presented, including generalized lymphoid
 hyperplasia, bronchiolitis and intersti-
 tial pneumonitis, marked cerebral edema,
 neuronal degeneration, and diffuse gliosis.
 The metabolism, biochemical activity, and
 excretion of amitriptyline are also
 discussed.

Stanford Medical Center
 Palo Alto, California

84 Rosenstein, Beryl J. & Engelman, Karl.
**Diarrhea in a child with a catechola-
 mine-secreting ganglioneuroma. Case report
 and review of the literature.** Journal of
 Pediatrics, 63:217-226, 1963.

This report describes a 15-month-old male
 patient with chronic diarrhea, flushing,
 and catecholamine-secreting ganglioneuroma.
 The patient was operated on for the removal
 of the neurogenic tumor; the left adrenal
 gland, to which the tumor was attached, was
 also removed. His recovery has been un-
 eventful, and the diarrhea and hypertension
 have ceased. A review of 78 patients with
 neurogenic tumors revealed that 7 had
 diarrhea or hypertension as a prominent
 feature. In conjunction with these case
 studies, special urine studies were con-
 ducted, and the DOPA, dopamine, norepineph-
 rine, and epinephrine were determined by
 the trihydroxyindole fluorimetric method
 after Dowex 50 column chromatography. All
 preoperative catecholamine values were
 distinctly elevated. Postoperatively, all
 values fell markedly, although the levels
 of DOPA and dopamine remained slightly

above normal controls. The secretion of
 catecholamines by neural tumors is con-
 sistent with the common background of
 sympathetic ganglion cells and cells of the
 chromaffin system.

The Johns Hopkins Hospital
 Baltimore, Maryland

1785 Ragheb, Moufid. **Parotid infection
 caused by dryness of mouth. Report
 of 3 cases after use of tranquilizers.**
 Geriatrics, 18:627-628, 1963.

Three cases of parotid infection caused by
 dryness of the mouth as a side reaction
 due to the use of tranquilizers is reported.
 The patients were female, aged 62, 83, and
 85 years, respectively, suffering from
 chronic brain syndrome secondary to arterio-
 sclerosis. Medication included trifluopro-
 mazine, benetropine, chlorpromazine, and
 amitriptyline. The 85- and 62-year-old
 patients recovered after deep X-ray therapy,
 while the 83-year-old died in two days from
 severe toxemia after treatment with peni-
 cillin. One uniform feature in these three
 cases is the use of tranquilizers before
 the onset of acute parotid infection. One
 of the three patients complained that food
 had no taste. All three complained of
 difficulty in swallowing food; these mani-
 festations can be explained by the diminution
 of salivary secretion. Tranquilizers
 should be used with caution in elderly
 patients.

Winnebago State Hospital
 Winnebago, Wisconsin

1786 Shaw, Edward B. **Analgesics and
 chronic renal disease.** Journal of
 the American Medical Association, 185(6):
 545, 1963. (Letter).

The author comments on an article and
 editorials (May 11 issue) regarding the use
 of analgesics in chronic renal disease. It
 was pointed out that the patient who con-
 sumes 10 to 30 analgesic tablets daily over
 a period of years will not profit from a
 warning on the label and scarcely deserves
 this protection. It was concluded that the
 real problem of the analgesics is not that
 outrageous dosage over a period of years
 will produce, as expected, unpleasant
 results but that over-reliance on these
 agents will obscure pain and fever symptoms,
 which deserve attention, not for symptomatic
 relief, but for definite diagnosis and
 treatment.

San Francisco, California

SIDE EFFECTS 1787-1791

- 1787 Robson, P. Emetics in poisoning. *Lancet*, 2(7309):689, 1963. (Letter).

Although emetics are ineffective in established barbiturate or phenothiazine poisoning, ipecacuanha-barbiturate tablets are being used. Ipecacuanha appears more effective than lavage or spontaneous emesis in removing ingested salicylate from dogs. Salt and ipecacuanha have caused death when, having been proved ineffective, they have not been immediately removed by lavage. In a case recently reported, death resulted from hypernatremia after an attempt to induce emesis with 2 doses of hypertonic saline in a person suffering from an overdose of perphenazine and imipramine. Emesis, mechanically or drug induced, is an excellent first aid measure when used within minutes of the ingestion of a toxic substance.

Farnborough, Kent, England

- 1788 Oltman, Jane E. & Friedman, Samuel. Protein-bound iodine in patients receiving perphenazine. *Journal of the American Medical Association*, 185(9):726-727, 1963.

The level of protein-bound iodine (PBI) was found to be elevated in 13 of a group of 50 chronically psychotic patients (29 males and 21 females) who had received perphenazine for periods ranging from 8 to 50 months. Patients who had received a total of more than 15,000 mg of perphenazine showed a higher incidence of elevated PBI. This finding was not accompanied by any clinical or laboratory evidence of hyperthyroidism. Preliminary data point to some quantitative alteration of thyroxin-binding alpha globulin in these cases.

Fairfield State Hospital
Newtown, Connecticut

- 1789 Nordstrom, Frank B. Death after withdrawal of meprobamate. *Journal of the American Medical Association*, 185(10):807, 1963. (Letter).

In commenting on a clinical note (June 8 issue) concerning death after withdrawal of meprobamate, the author points out an

alternate final diagnosis. The symptoms that occurred (profuse sweating, coarse tremors of the extremities, apprehension leading to convulsion, hypertension developing into hypotension, and oliguria) could have been attributed to water intoxication. In a reply from one of the authors of the article in question, the reasons for excluding water intoxication as a diagnosis were stated. It was concluded that hyperthermia, to the degree observed in this patient who died after meprobamate withdrawal, was not associated with water intoxication.

Farmington, New Mexico

- 1790 Hollister, Leo E. & Bennett, J. L. Thyroid function and psychotherapeutic drugs. *Journal of the American Medical Association*, 183(10):890, 1963. (Letter).

Comment is made on a report of progressive elevation of serum protein-bound iodine (PBI) in four patients being treated with perphenazine. Determinations of PBI were obtained at various time periods for 42 patients treated for at least 6 weeks with a combination of perphenazine and amitriptyline. Dosages up to 64 mg of perphenazine and 200 mg of amitriptyline daily were used. All PBI levels fell within the ordinary ranges of normal (4.0 to 8.0 µg/ml). Mean levels for PBI were 5.7 µg/100 ml at the beginning of treatment and 5.4 µg/100 ml at the end of 6 weeks. There was a nonsignificant change in serum cholesterol levels. Previous studies failed to demonstrate any changes in thyroid tests from chlorpromazine used alone in doses of 100 to 400 mg daily or in combination with dextroamphetamine, imipramine, isocarboxazid, and trifluoperazine. There is still little evidence for a confounding effect on PBI, or any other test of thyroid function, resulting from any antipsychotic or antidepressant drug.

Palo Alto, California

- 1791 Swanson, Leonard A. & Okada, Tsuyoshi. Death after withdrawal of meprobamate. *Journal of the American Medical Association*, 184(10):780-781, 1963.

This paper reports a case of meprobamate addiction in a 38-year-old man, who, when withdrawn from the drug, developed anxiety,

hyperhydrosis, tremor, hyperpyrexia, and grand mal seizures, and died. When first hospitalized, the patient complained of nervousness, sweating, and mild tremors. It was learned that the patient was on a regimen of 400 mg of meprobamate q.i.d. for nervousness. Urinalysis on admission revealed a specific gravity of 1.010, a few white blood cells, and negative results to tests for albumin, sugar, acetone, and bile. On the second hospital day, urinalysis demonstrated a specific gravity of 1.018 and 3+ albumin. It was negative for bile, but urobilinogen was present in a dilution of 1:50. Throughout the day the patient's temperature remained elevated despite cooling measures and reached a maximum of 107.8° F rectally approximately 2 hours after admission. A blood count obtained at this time revealed a white-blood-cell count of 14,800/cu mm, a hemoglobin level of 20.0 gm %, and a packed-cell volume of 57%. During the first night, the patient was restless and unable to sleep, and received 1,000 ml of 5% dextrose in water i.v. Fourteen hours after admission, the patient had a grand mal seizure, which was controlled with 2 ml of 50% magnesium sulfate and 250 mg of pentobarbital administered i.v. The patient died 68 hours after admission. The results of this case show that a patient with meprobamate addiction should be withdrawn from the drug slowly. If convulsions occur, dosage should be increased and then again reduced over a longer period.

Los Angeles County Harbor General Hospital
Los Angeles, California

92 Friend, Dale G. **Analgesic abuse and renal toxicity.** (Editorial) *Journal of the American Medical Association*, 184(6): 5-496, 1963.

The analgesic abuse and renal toxicity of phenacetin, when used in combination with acetylsalicylic acid for mild pain, are reviewed. It is believed that this drug mixture produces synergistic effects and that a more potent analgesic effect occurs with these drugs than with single drugs given in full dosages. The ease with which phenacetin and acetylsalicylic acid can be obtained, the continual advertising to the public, and the belief that these drugs are not toxic have led to a certain amount of abuse. When used over long periods,

phenacetin and acetylsalicylic acid can cause gastrointestinal tract irritation, indigestion, and pyrosis. No serious toxic effects have been described for caffeine, although it can cause CNS stimulation (insomnia may occur) and mild diuresis. It is suggested that a widespread education program be developed as a warning against the abusive use of these analgesic combinations and that all such preparations should carry labels recommending no more than six tablets in 24 hours and the avoidance of continued use.

Boston, Massachusetts

See also: 1622, 1641, 1644, 1645, 1646, 1647, 1648, 1649, 1650, 1652, 1654, 1655, 1666, 1667, 1668, 1671, 1673, 1684, 1688, 1699, 1805, 1824

BEHAVIORAL STUDIES

- 1793 Aceto, M. D. G., Kinnard, W. J., & Buckley, J. P. Effects of compounds on blood pressure and behavioral responses of rats chronically subjected to an avoidance-escape situation. *Archives Internationales de Pharmacodynamie et de Therapie*, 144(1-2):214-225, 1963.

Male Wistar rats, 300 to 400 g in weight, were tested in an automatic rat-pole-climbing apparatus for latency of response under drugged and control conditions. Chlorpromazine (5.0 mg/kg), reserpine phosphate (0.5 and 1.5 mg/kg), and JB-329 (15 mg/kg) inhibited response; d-amphetamine sulfate (0.75 and 1 mg/kg) and N-ethyl-3-piperidyl-phenylcyclopentyl glycolate HCl (0.25 mg/kg) facilitated response; and 5-(0-methoxyphenoxyethyl)-2-oxazolidone had no effect. The stress induced by the apparatus caused a rise in blood pressure which was slightly reduced by reserpine (0.5 to 1.5 mg/kg) and chlorpromazine (5 mg/kg) but was unaffected by the other drugs.

University of Pittsburgh School of Pharmacy
Pittsburgh 13, Pennsylvania

- 1794 Swinyard, Ewart A., Castellion, Alan W., Fink, Gregory B., & Goodman, Louis S. Some neurophysiological and neuropharmacological characteristics of audiogenic-seizure-susceptible mice. *Journal of Pharmacology and Experimental Therapeutics*, 140(3):375-384, 1963.

Audiogenic-seizure-susceptible male albino mice (0¹ Grady strain) and male albino mice (CF #1 strain) not susceptible to audiogenic seizure were subjected to a battery of well-standardized, seizure-evoking techniques, and their responses were interpreted in terms of underlying neurophysiological mechanisms. Audiogenic seizures were induced by means of an electric doorbell, and pentylenetetrazol seizure threshold, maximal-electroshock seizure threshold (a.c. MES), minimal-electroshock seizure threshold (a.c. ES), and low-frequency

electroshock (l.f. ES) threshold were determined. The patterns (pretonic, tonic, and terminal clonus) of maximal audiogenic seizures (MAS) induced by supramaximal electroshock, i.v. pentylenetetrazol, and sound were quite similar. Convulsions were induced by the tenth postnatal day and reached maximum incidence and severity by the twenty-second day, after which the incidence of MAS decreased with increased age and weight. Audiogenic-susceptible mice were more sensitive to electroshock and more resistant to the threshold lowering effects of hyponatremia than the controls (CF #1 strain). Pentylenetetrazol produced no significant differences in the susceptibility of audiogenic-seizure mice and controls. MAS animals were more susceptible to electroshock tonic-clonic convulsions than submaximal audiogenic-seizure or control animals. A longer latency for MES was shown by submaximal audiogenic-seizure mice than by MAS or control animals. Trimethadione, phenobarbital, diphenylhydantoin, and meprobamate abolished the tonic-extensor component of MES in CF #1 mice at the following respective dosages: 1,190 mg/kg, 30 mg/kg, 14.4 mg/kg, and 187 mg/kg. These drugs were about three times more potent against the tonic-extensor component of MAS in CF #1 mice than against the same component of MES in albino mice of both sexes (Fringo strain). Reserpine (> 165 mg/kg) had no effect on this component of MAS or MES, while chlorpromazine (21 mg/kg) was effective against the MES tonic-extensor component.

University of Utah College of
Pharmacy and College of Medicine
Salt Lake City, Utah

- 1795 Roszkowski, Adolph P. & Kelley, Nancy M. A rapid method for assessing drug inhibition of feeding behavior. *Journal of Pharmacology and Experimental Therapeutics*, 140(3):367-374, 1963.

A simple quantitative test procedure for evaluating the anorexigenic potential of drugs in rats was described. Male Sherman

and Holtzman rats (250 to 658 g) were given anorexigenic drugs p.o., and their potential was evaluated in ml/kg of beef broth consumed. Of the 10 drugs tested 4 are very potent: *d*-amphetamine (2.8, 5.7, 11.4 mg/kg), methamphetamine (4.0, 8.0, 16.0 mg/kg), 2-amino-4-methyl-5 phenyl oxazoline (6.0, 9.0, 12.0 mg/kg), and 2-amino-5-phenyl oxazoline (4.0, 8.0, 10.0 mg/kg). The intermediate-potency group consisted of dl-amphetamine (6.3, 7.9, 15.8 mg/kg), diethylpropion (14.0, 18.7, 23.3, 28.4 mg/kg), and methylphenidate (8.7, 17.4, 52.0, 104.0 mg/kg). The l-amphetamine (43.3 mg/kg) was inactive, whereas fenmetrazine (49.8, 99.6 mg/kg) and phenmetrazine (42.0, 84.0 mg/kg) displayed slight potency. The oxazolines were as potent as *d*-amphetamine, but were longer acting. At effective dose levels all of the anorexigens showed a similar degree of S stimulation. These results suggested that this quantitative test procedure (beef broth consumption) has as an end point preferential feeding behavior and may be a test that measures drug-induced depression of appetite.

Neil Laboratories, Inc.
Fort Washington, Pennsylvania

96 Hill, Harris E., Haertzen, Charles A., Wolbach, Albert B., Jr., & Miner, Edward J. The Addiction Research Center Inventory: Standardization of scales which evaluate subjective effects of morphine, amphetamine, pentobarbital, alcohol, LSD-25, pyrahexyl and chlorpromazine. *Psychopharmacologia*, 4:167-183, 1963.

The Addiction Research Center Inventory (RCI), comprised of 550 items for evaluating subjective drug effect and personal characteristics, was standardized using 219 former narcotic addicts on a number of drug conditions. Sixty-five subjects were white, and 154 were Negro, with mean ages of 30.2 and 28.8 years, respectively, and a mean I.Q. of 106. The inventory was administered under no drug and placebo, morphine (10 and 20 mg i.m.), pentobarbital (200 and 250 mg i.m.), chlorpromazine (day 1, 25 mg q.i.d.; day 2, 50 mg q.i.d.; day 3, 75 mg once), LSD-25 (60 and 1.5 µg/kg p.o.), pyrahexyl (60 and 90 mg p.o.), dl-amphetamine (15 and 30 mg i.m.), and alcohol-30% (1.1, 2.12, 4.0, and 4.43 cc/kg p.o.). Since nonsignificant differences were found when scoring each of the drug scales separately on the

no-drug and placebo conditions, these data were combined for standardizing all scales. Validity generalization, dose-effect, and retest studies showed that the drug scale possessed a high degree of validity and reliability, but the placebo scale lost discrimination in the validity generalization group.

National Institute of Mental Health
Addiction Research Center
Lexington, Kentucky

1797 Weiss, Bernard & Laties, Victor G. Effects of amphetamine, chlorpromazine and pentobarbital on behavioral thermoregulation. *Journal of Pharmacology and Experimental Therapeutics*, 140(1):1-7, 1963.

The effects of amphetamine, chlorpromazine, and pentobarbital on thermoregulatory behavior have been determined in four studies: three examined the effects of the drugs on behavior maintained by the delivery of heat, and the fourth examined the effects of the drugs on temperature fall in the cold. Adult, male albino rats of the Sprague-Dawley strain were trained to warm themselves in the cold by pressing a lever that turned on a heat lamp. Amphetamine (2 mg/kg) increased the frequency with which the lamp was turned on even though the skin temperature was driven above normal. Chlorpromazine (2 mg/kg) enhanced the rate at which temperature fell in the cold, but there was no compensatory rise in the rate at which the rat turned on the heat lamp. Pentobarbital (less than 20 mg/kg) led only to a transient fall in the rate at which the heat lamp was turned on. Both amphetamine and chlorpromazine were found to impair behavioral regulation by increasing and decreasing, respectively, the optimal frequency of bursts of heat.

The Johns Hopkins University
School of Medicine
Baltimore, Maryland

1798 Smith, Charles B. Enhancement by reserpine and α -methyl dopa of the effects of *d*-amphetamine upon the locomotor activity of mice. *Journal of Pharmacology and Experimental Therapeutics*, 142(3):343-350, 1963.

The locomotor activity of male albino mice of the Swiss-Webster strain was studied

under the following conditions: pretreatment with reserpine (5 mg/kg) or with *L*- α -methyldopa (400 mg/kg) followed by an injection of *D*-amphetamine (dosage range 1 to 100 mg/kg) at 3, 8, 24, 80, and 240 hours; reserpine (5 mg/kg) followed by cocaine or pipradrol (dosage range 1 to 100 mg/kg) 24 hours after reserpine; and *L*- α -methyldopa (400 mg/kg) followed by *L*-DOPA (dosage range 10 to 1,000 mg/kg) 24 hours after *L*- α -methyldopa was injected i.v.; all other injections were i.p. Enhancement of the activity-increasing effect of *D*-amphetamine occurred 24 hours after reserpine and was greatest 80 hours after reserpine. Marked enhancement of the activity-increasing effect of *D*-amphetamine occurred 8 hours after *L*- α -methyldopa and lasted for at least 80 hours. Neither the effect of cocaine nor of pipradrol was enhanced 24 hours after reserpine, which indicates the specificity of the enhancement of the effect of *D*-amphetamine by reserpine. Doses of *L*-DOPA ranging from 30 to 170 mg/kg decreased locomotor activity 24 hours after the administration of *L*- α -methyldopa; doses of *L*-DOPA ranging from 300 to 1,000 mg/kg increased locomotor activity 24 hours after *L*- α -methyldopa. The LD₅₀ of *D*-amphetamine was estimated after treatment with reserpine and with *L*- α -methyldopa at 3, 8, 24, 80, and 240 hours. Reserpine causes a depletion of 5HT, dopamine, norepinephrine of equal duration. *L*- α -Methyldopa produces only a transient depletion of 5HT and dopamine, but a more prolonged depletion of norepinephrine.

Harvard Medical School
Boston, Massachusetts

- 1799 Goldman, Allen S. & Yakovac, William C. The enhancement of salicylate teratogenicity by maternal immobilization in the rat. *Journal of Pharmacology and Experimental Therapeutics*, 142(3):351-357, 1963.

Experiments were conducted to determine whether the maternal systemic stress produced by immobilization enhances the teratogenicity of sodium salicylate poisoning in pregnant rats and to determine whether such an altered maternal state is sufficient to cause low, nonteratogenic doses of the salicylate to produce anomalies. Three hundred virgin, female albino rats, 8 to 9 weeks of age, were mated and subjected to the following treatments 10

days after gestation: single s.c. injections of sodium salicylate; immobilization; and single s.c. injections of salicylate and immobilization. Dosage, duration of immobilization, and time of injection fraction are tabulated. The effects of treatments were measured and tabulated according to the following classification: maternal death; maternal morbidity; fetal mortality; fetal morbidity; and fetal abnormality. The 629 fetuses were examined grossly after Caesarean delivery on the twentieth day. The anomalies produced by salicylate with or without immobilization consist of dorsal midline, ventral midline, and eye defects. These congenital anomalies do not occur after immobilization alone up to 8 hours in duration or with doses of salicylate alone of 300 mg/kg. Significant numbers of these anomalies are produced by 400 and 500 mg/kg of salicylate. When salicylate is administered during immobilization, there is a marked elevation in the rate of anomalies and a significant increase of live litters with abnormal fetuses produced by the teratogenic doses of salicylate. Immobilization for 2-1/2 or 4-1/2 hours, combined with 300 mg/kg salicylate, produced a significantly high incidence of anomalous fetuses.

University of Pennsylvania
School of Medicine
Philadelphia, Pennsylvania

- 1800 Domino, Edward F., Karoly, Andrew J., & Walker, Edward L. Effects of various drugs on a conditioned avoidance response in dogs resistant to extinction. *Journal of Pharmacology and Experimental Therapeutics*, 141(1):92-99, 1963.

The differential effects of various drugs were determined in dogs that were resistant to extinguishing an instrumental conditioned flexion response. Six adult male mongrel dogs (10 to 20 kg) were trained with a conditioned stimulus (CS) ("beating" tone of about 10,000 cps) and an unconditional stimulus (US) (0.7 milliamperes pulsating d.c. shock) to lift their left foreleg about 8 cm within the CS-US 5-second interval to avoid shock. After reaching a criterion of 19 out of 20 successful avoidance responses, the animals were again given 200 extinction trials. All animals made 100% avoidance responses during the extinction series. During the drug-testing sessions, chlorpromazine (2, 4, and 8 mg/kg s.c.), perphenazine

hydrochloride (0.5, 1, and 2 mg/kg s.c.), morphine sulfate (2, 4, and 8 mg/kg s.c.), meprobamate (50, 100, and 200 mg/kg p.o. after a 24-hour fast), phenobarbital sodium (25, 50, and 75 mg/kg p.o.), or reserpine (25, 50, and 100 mg/kg i.v.) were administered after a control series of 10 trials, and 1 or 2 hours before 10 retest trials or drug effects. A minimum of 12 days was allowed between each test session to minimize drug interaction effects. Chlorpromazine, perphenazine, and reserpine blocked the conditioned responses at all doses tested and caused minimal-to-no neurological deficit. Morphine showed minimal depressant effects on avoidance behavior. Meprobamate and phenobarbital in large doses produced blocked escape response as much as avoidance response and also produced neurologic deficit. Average shock currents of 3.5 and 7.0 milliamperes better dissociated avoidance from escape behavior after meprobamate than after phenobarbital.

University of Michigan
Ann Arbor, Michigan

1801 Banerjee, R. N. **Prevalence of habit forming drugs and smoking among the college students—A survey.** *Indian Medical Journal*, 57(8):193-196, 1963.

A survey of drug and smoking habits of 1,132 college students of Calcutta University was reported. Amphetamines (methylphenidate, d-amphetamine, and other "pep" pills) were used by students (11.4%) to keep them awake, and none showed any addiction. Students who took drugs without medical advice comprised 20.4% of the population. Cigarette smokers included 26.0% of the students, and 15.7% were habitual smokers. No significant difference was shown in a comparison of the drug habit and smoking habit in the residential and non-residential students. It was concluded that, at the present time, there is no cause for alarm regarding the drug habit among the college students.

Calcutta University
Calcutta, India

1802 Smith, Gene M., Weitzner, Martin, Levenson, Sandra R., & Beecher, Henry K. **Effects of amphetamine and secobarbital on coding and mathematical performance.** *Journal of Pharmacology and Experimental Therapeutics*, 141(1):100-104, 1963.

This investigation was performed to study the effects of amphetamine sulfate and secobarbital on a specific type of high-level intellectual performance (solving of calculus problems), to study the effects of the two drugs on subjective states, and to verify the usefulness of the digit-letter coding test, which is sensitive to the mental impairment produced by opiates. Amphetamine sulfate (14 mg/70 kg body weight) was administered twice, secobarbital sodium (50 mg/70 kg) once, and placebos twice to 78 male graduate and undergraduate students (18 to 31 years of age). The double-blind technique was used in the oral administration of the five visually identical capsules. On each of the 5 experimental days, a subject was given a mood and feeling checklist, a 60-minute test of intermediate calculus, a 4-minute digit-letter coding test, and another mood and feeling checklist. The subjective effects of secobarbital were much less dramatic than those of amphetamine. Thirty-seven of the 81 items revealed significant amphetamine effects, whereas only 7 items revealed significant secobarbital effects. Secobarbital impaired performance on both of the objective tests. Amphetamine did not influence performance on the calculus test, but it facilitated performance on the coding test. The effect of amphetamine on coding performance was taken as further evidence for the general usefulness of the digit-letter coding test in psychopharmacological studies of human subjects.

Massachusetts General Hospital
Boston, Massachusetts

1803 Smith, Gene M., Weitzner, Martin, & Beecher, Henry K. **Increased sensitivity of measurement of drug effects in expert swimmers.** *Journal of Pharmacology and Experimental Therapeutics*, 139(1):114-119, 1963.

The effects of amphetamine and of secobarbital on the performance of 15 nonexpert swimmers and 15 expert swimmers were compared. In the expert study, three subjects swam the 100-yard free style, three the 100-yard butterfly, three the 200-yard free

style, three the 200-yard backstroke, and three the 200-yard breast stroke. In the nonexpert study the groups were the same, except that a 100-yard breast stroke was substituted for the 100-yard butterfly. Each subject swam his event twice a day for 2 days under a given swimming condition (rested-solo, fatigued-solo, rested-group, and fatigued-group) and medication condition (amphetamine, 14 mg/70 kg of body weight; secobarbital, 100 mg/70 kg, and placebo). Amphetamine improved the performance of experts and nonexperts to similar degrees. Secobarbital impaired the performance of both groups, possibly more so with experts than nonexperts, but this was not conclusive. The greater sensitivity due to precision of measurement was provided by the experts as compared to nonexperts. It would have been necessary to increase the nonexpert sample to about 80 subjects to obtain precision equal to that provided by the 15 expert swimmers.

Harvard Medical School at the
Massachusetts General Hospital
Boston, Massachusetts

- 1804 Moore, Kenneth E. Toxicity and catecholamine releasing actions of d- and l-amphetamine in isolated and aggregated mice. *Journal of Pharmacology and Experimental Therapeutics*, 142(1) 6-12, 1963.

The toxicity and catecholamine-releasing action of d- and l-amphetamine were studied in isolated and in aggregated mice. Male albino mice (20 to 30 g in weight) were administered d- or l-amphetamine (10 to 300 mg/kg i.p.) in a constant volume of 1 ml/100 g body weight. The mice were then placed in cages, four mice per cage in the aggregated series; one per cage in the isolated series. After 4 hours, their heart, brain, and adrenals were removed for catecholamine determinations. Under both isolated and aggregated conditions, d-amphetamine was more toxic than the l-isomer. In isolated mice, d-amphetamine reduced the norepinephrine content in the heart and brain, but had little effect upon the adrenal content of catecholamines. Higher doses of l-amphetamine produced similar effects. Aggregation enhanced the norepinephrine depleting action of d-amphetamine but not of l-amphetamine. It was suggested that the release of endogenous stores

of norepinephrine plays a role in the enhanced toxicity of d-amphetamine in aggregated mice.

Dartmouth Medical School
Hanover, New Hampshire

- 1805 Hardinge, Mervyn G. & Peterson, Donald I. The effects of exercise and limitation of movement on amphetamine toxicity. *Journal of Pharmacology and Experimental Therapeutics*, 141(2):260-265, 1963.

The effects of forced exercise and limitation of movement on the toxicity of amphetamine in isolated, aggregated, and closely grouped or crowded mice were studied at environmental temperatures of 20°, 26°, and 32° C. Male Swiss-Webster mice (19 to 21 g in weight) were used in all experiments. To determine the LD₅₀ of amphetamine, a minimum of 18 mice was employed for each environmental condition tested. Elevation of temperature increased amphetamine toxicity. An aggregation effect was noted only at a temperature of 26° C. An increase in amphetamine toxicity at 20° C was produced by forced exercise. At 26° C, the effect on isolated animals of forced exercise was as great as the effect of aggregating animals. Factors that increase heat production or decrease heat loss tend to increase amphetamine toxicity.

Loma Linda University School of Medicine
Loma Linda, California

- 1806 Wallgren, Henrik & Tirri, Rauno. Studies on the mechanism of stress-induced reduction of alcohol intoxication in rats. *Acta Pharmacologica et Toxicologica*, 20:27-38, 1963.

A variety of experiments were performed to help elucidate the mechanism of stress-induced reduction of alcohol intoxication. Male rats, approximately 4 months old, were used in all experiments but one, in which 11-week-old female rats were used. Alcohol was always administered i.p. as a 10% (weight/volume) solution in saline. The tilted-plane technique was used to assess the state of intoxication. The pharmacological agents used were: alcohol, adrenaline, and amphetamine sulfate. After 2 mg alcohol/g had been given i.p., vigorous

exercise radically improved the performance of the rats in a simple functional test. Other forms of stress---electric shocks and loud noise---had less effect. Hypophysectomized rats reacted as strongly as normal rats. Experiments with adrenaline and amphetamine, the latter improving performance as much as the muscular work, suggest that an arousal reaction is involved. The brain-stem reticular activating system is insensitive to alcohol but, with moderate doses, the effect is largely reversible. The effect of exercise was diminished and that of amphetamine blocked after i.p. Injection of 3 mg alcohol/g, indicating that there is a threshold dose of alcohol above which the arousal reaction is difficult to achieve.

tate Alcohol Monopoly
Helsinki, Finland

1807 Rogers, Larry A., Alcantara, G. A., & Fouts, James R. *p*-Aminosalicylic acid induced prolongation of hexobarbital sleeping time. *Journal of Pharmacology and Experimental Therapeutics*, 142(2):242-247, 1963.

The effect of *p*-aminosalicylic acid (PAS)-induced glycogen infiltration of the hepatic cells on the duration of hexobarbital action in vivo and on the metabolism of hexobarbital, aminopyrine, and codeine by hepatic microsomes in vitro was studied. Male, white Holtzman rats (75 to 125 g in weight) received PAS i.p. 3, 12, 24, and 48 hours before hexobarbital sodium (100 mg/kg i.p.) was administered. Sleeping time was considered to be the time in minutes during which the righting reflex was absent. Metabolic pathways studied were the side-chain oxidation of hexobarbital, *O*-dealkylation of codeine, and the *N*-dimethylation of aminopyrine. Animals maintained on a 5% PAS diet exhibited prolonged hexobarbital sleeping time, apparently because of a decreased ability to eliminate the anesthetic. The defect in drug-metabolizing activity in livers from PAS-treated animals was localized in the microsome. Routine administration had no effect on hexobarbital sleeping time, and the in vitro addition of PAS to drug-metabolizing enzyme systems was not inhibitory. The possibility of correlation between hepatic glycogen level, structure of the smooth-surfaced endoplasmic reticulum, and the activity of certain microsomal enzymes is discussed.

tate University of Iowa
Iowa City, Iowa

1808 Soušková, M. & Benešová, O. *Ovlivnění orientační reakce u krys imipraminem, chlorpromazinem a fenmetrazinem. (The effect of imipramine, chlorpromazine and phenmetrazine on orientation in rats.)* *Activitas Nervosa Superior*, 5:177, 1963.

A test was made of several groups of 8 or 9 male white rats, each, weighing 300 to 400 g, that had been selected from a population of 120 animals on the basis of extremes of frequency of the erection reaction. The effects of drugs on this frequency, on grooming movements, on the duration of immobility, and on the running of a two-chamber cage test were recorded. The more excitable rats were inhibited by doses of 2 mg/kg and 10 mg/kg chlorpromazine. The less excitable rats when given the lower dose of chlorpromazine were still more mobile than when given physiological solution. The reduction in activity produced by the higher dose in this group was less than that produced by a similar dose in the more excitable rats. Phenmetrazine in doses of 2 and 10 mg/kg considerably increased the motor activity of both groups in comparison to physiological solution. There was a greater increase in the less excitable rats, and the difference between the two groups was statistically significant. Imipramine (2 mg/kg) produced an increase in orienting activity of the less excitable rats, but resulted in an increase in the total activity of the excitable rats. Physostigmine (0.5 mg/kg), on the other hand, reduced only the orienting activity of animals with low excitability, while in the more excitable group motor activity was markedly depressed in regard to all parameters.

Charles University
Prague, Czechoslovakia

1809 Bovet, Daniel & Amorico, Luigi. *Effet de l'amphétamine sur une réaction conditionnée d'évitement au cours d'un exercice prolongé. (Effect of amphetamine on a conditioned avoidance reaction during prolonged exercise.)* *Academie Des Sciences*, 256:3901-3904, 1963.

An experiment was devised to study prolonged conditioned behavior in the rat, and to study the effect of amphetamine on the conditioned responses. Conditioned rats were subjected to a succession of tests lasting 30 seconds each, the conditioned stimulus (light) preceding the unconditioned

stimulus (electric shock) by 5 seconds. The experiment consisted of consecutive trials over a 6-day period allowing only for a 40-minute daily rest, during which the animal was allowed to eat at will. The brief rest period had the effect of improving performance in the tests immediately following. Amphetamine, when administered, also improved performance. It was concluded that in a rat subjected to prolonged exercise, changes in performance precede the decrease of general motor activity. When new factors (i.e. food, amphetamine) are introduced and the exercise is begun again, depression of alertness seems to be inhibited.

Istituto Superiore di Sanita
Rome, Italy

1810 Brimblecombe, R. W. Effects of psychotropic drugs on open-field behaviour in rats. *Psychopharmacologia*, 4: 139-147, 1963.

Rats were studied in Hall's open-field test 1-1/2 or 3 hours after various doses of the following 10 psychotomimetic drugs: LSD-25; mescaline sulfate; harmine hydrochloride; *N*-methyl-3-piperidyl benzilate hydrochloride; dimethyltryptamine; diethyltryptamine; di-propyltryptamine; α -methyltryptamine; bufotenine bioxalate; and phencyclidine. After eight of these, changes in behavior at the lowest effective dose included significant decrease in emotional defecation. Harmine, at a higher dose level, also had this effect, but with dimethyltryptamine it did not occur at any dose level. Three stimulant drugs (pipradrol, amphetamine, and phenelzine) and five depressant drugs (pentobarbital, methylpentynol, thiopropazate, chlorpromazine, and reserpine) were also tested, but no consistent pattern of activity emerged. Among tranquilizers tested, thiopropazate and reserpine decreased all types of behavior, while chlorpromazine decreased rearing and ambulation. The sedative pentobarbital decreased ambulation alone, while the hypnotic methylpentynol decreased only defecation. Among stimulants, amphetamine increased ambulation while phenelzine decreased it, and pipradrol affected only defecation. The lowest doses

of all drugs causing changes in open-field behavior were 1-1/2 to 20 times higher than the accepted human doses, except with LSD-25 where the ratio was 1:250 to 1:500 and reserpine where it was 1:100.

Chemical Defence Experimental Establishment
Porton Down, Salisbury, England

1811 Domino, E. F. Tranquilizers and competitive sports. *Journal of the American Medical Association*, 186(2):173-174, 1963.

A question is asked concerning which tranquilizers could be used by competitive sportsmen or athletes to allay anxiety without diminishing reflex time. The reply states that the disruptive effects of stress on performance of a perceptual motor task are reduced by small doses of sedative and tranquilizing drugs, such as meprobamate and phenyltoloxamine; barbiturates, such as pentobarbital and secobarbital; and phenothiazine derivatives, such as promazine and chlorpromazine. However, verbal reassurance to allay anxiety is to be preferred to drug therapy for participants in competitive sports; where that is ineffective, then small doses of meprobamate (400 mg) or chlordiazepoxide (10 mg) administered orally are indicated.

Ann Arbor, Michigan

1812 Seevers, M. H. Amphetamine and alcohol. *Journal of the American Medical Association*, 184(10):843, 1963.

A question is asked regarding changes to be expected in human behavior following simultaneous ingestion of ethyl alcohol and amphetamine sulfate. The reply states that, pharmacologically, simultaneous ingestion of ethyl alcohol and amphetamine sulfate would be expected to antagonize the depressant effects of alcohol. This could prolong the duration of abnormal behavior. The abuse of large amounts of amphetamine with alcohol worsens rather than corrects delirium tremens.

Ann Arbor, Michigan

813 Altschule, Mark D. Amphetamine and performance. Journal of the American Medical Association, 185(6):549, 1963.

A question is asked concerning the effects of amphetamine on mental and motor efficiency. The reply states that amphetamine and its derivatives are used to minimize sleepiness. Amphetamine affects performance in nontoxic doses by preventing a sleepy person from falling asleep, but there is no good evidence that it changes the performance of an awake, but sleepy, person to that of an awake and rested person.

Waverley, Massachusetts

See also: 1633, 1647, 1817

PHARMACOLOGY

1814 Rutishauser, Markus. **Beeinflussung des kohlenhydratstoffwechsels des Rattenhirns durch Psychopharmaka mit sedativer Wirkung. (Influencing carbohydrate metabolism of the rat brain through psychopharmacological agents with sedative action.)** Naunyn-Schmiedeberg's Archiv für Experimentelle Pathologie und Pharmakologie, 245:396-413, 1963.

In rats treated with sedative doses of various drugs, alteration of glucose, pyruvate, and lactate were measured in blood and brain and compared to that of body temperature and general behaviour. Chlorpromazine, reserpine, the benzoquinolizine derivative Ro 4-1284, chlordiazepoxide, and morphine induced the following changes: (1) short-lasting increase of glucose in blood and brain as well as of the brain-blood ratio; (2) short-lasting increase of pyruvate and lactate in blood, although not in brain, resulting in a drop of the brain-blood ratio; and (3) increase of the approximated intracellular glucose concentration of brain, but decrease of pyruvate concentration. The maximum changes of carbohydrate metabolism in blood coincided with the beginning of sedation, whereas the alteration of the intracellular concentrations rather paralleled the central depression. Phenobarbital and methyprylone caused the following alterations: (1) increase of glucose in blood and brain that resembled those induced by the first group of drugs, but were of shorter duration or lower degree; (2) decrease of pyruvate and lactate in blood and brain resulting in an increased brain-blood ratio, in contrast to the first group of psychopharmaka; and (3) increase of the approximated intracellular glucose concentration in brain and decrease of pyruvate concentration, similar to the first group of drugs. The changes of carbohydrate metabolism in blood and brain paralleled fairly well those of hypothermia and hypnosis. Prevention of hypothermia did not abolish the alteration of carbohydrate metabolism, and hypothermia induced by cold environment was without effects on carbohydrate metabolites.

Medical Research Division of
Hoffmann-La Roche & Company, Inc.
Basel, Switzerland

1815 Marti, M. **Progesteronkonzentration im Blut unter hochdosiertem Relaxans Librium. (Progesterone concentration in the blood under large doses of the uterine relaxant Librium.)** Gynaecologia, 155:48-54, 1963.

Large doses chlordiazepoxide were given i.m. to patients with imminent abortion and labor, and the progesterone concentration in plasma was estimated before and after application. Although no changes take place in patients with normal progesterone concentration in the blood after chlordiazepoxide, progesterone increases in half of the cases with low progesterone concentration in plasma. Because of the decline of the progesterone concentration in blood after i.v. administration of that substance, a disturbance of liver metabolism is not probable, but an improved vascularization of the placenta after chlordiazepoxide is assumed.

University Women's Clinic
Basel, Switzerland

1816 Appel, E. **Distributia acetilcolinesterazei in creierul uman. Distribution of acetylcholinesterases in the human brain.** Studii si Cercatari de Neurologie, 8(2):249-257, 1963.

The distribution of acetylcholinesterase was studied in the brain of a child (1 to 1-1/2 years old), 10 hours after death. Intense activity was noted in the nerve nuclei of the cerebral trunk; in the olivary body and in the reticular matter. A weaker activity was noted in the red nucleus and in the nigra substance. Negative reactions to the Gomori technique were noted in the white substance of the cerebellum, whereas the main routes of conduction, the origin of the staples and fasciculus, the exterior and the nuclei of the cerebellum, the putamen, striatum, globus pallidus, amygdalian nucleus, thalamus, and hypothalamus, showed positive reactions. In the positive regions, the following was observed: (1)

the localization of the enzyme only in the body of nerve cells; (2) activity in the synaptic junctions, the cell surface, at the base of the extensions, and between neurons, while the cell bodies were negative; or (3) another type of localization existing simultaneously both in the nerve cell and at the synaptic terminations. In the exterior of the cerebellum, a marked difference appeared between the aleocortex and the neocortex, and cholinergic nerve fibrils on the blood vessels were noted.

Institute of Neurology
Academy of I.P. Pavlov, R.P.R.

1817 Goldenberg, M. A. & Korolenko, T. P.
Alcoholic "psychopathological" syndromes in experimental animals. Zhurnal Evropejskoi Psikiatrii imeni S.S. Korsakova, 63:1861-1866, 1963.

Various forms of general behavior disorders during acute and chronic alcoholic intoxication were studied in 14 dogs to enable understanding of the pathogenesis of alcoholic disorders in man. More than 600 observations were made. Each dog was given alcohol almost every day for 1 to 6 months. Because dogs generally refuse alcohol, 1 ml of 40% alcohol solution per kilogram was mixed with food. This dosage was increased very slowly. Refusal of alcohol by a dog necessitated starting over again, using a stomach tube. Large doses (6 to 8 ml of 40% solution/kg) produced within 5 or 10 minutes a syndrome resembling alcoholic stupor in man, which gradually deepened. Two young dogs exhibited clonic epileptic convulsions while in the comatose state. At average doses of 2 to 4 ml, an increase in motor activity was usually observed. Acute alcoholic intoxication produced soporific and comatose states, and a peculiar syndrome of psychomotor excitation with elements of euphoria. The type of nervous constitution of the animal undoubtedly played an important part in the development of these phenomena. Upon extended (4 to 6 months) intoxication, six of the dogs became more mobile and somewhat uninhibited, including one previously "phlegmatic" dog. With continued intoxication, deeper changes gradually developed: acute excitation, irritability, aggression, increased sensitivity to sounds, light tremor, alcoholic delirium, and hallucinations, resembling to a certain degree the syndrome of alcoholic encephalopathy.

Leningrad Medical Institute
Leningrad, U.S.S.R.

1818 Stille, G., Ackermann, H.,
Eichenberger, E., & Lauener, H.
Vergleichende pharmakologische Untersuchung eines neuen zentralen Stimulans, 1-*p*-Tolyl-1-oxo-2-pyrrolidino-*n*-pentan-HCl (Comparative pharmacological study of a new central stimulant, 1-*p*-tolyl-1-oxo-2-pyrrolidino-*n*-pentane HCl.) Arzneimittel-Forschung, 13: 871-877, 1963.

The compound 1-*p*-tolyl-1-oxo-2-pyrrolidino-*n*-pentane-HCl (F-1983) is a central stimulant which differs from amphetamine in some important respects: F-1983 intensifies the fighting tendency of mice several times even when given in doses following which no appreciable increase in motility can be recorded. By contrast, amphetamine raises drive in the fighting test only after doses which considerably increase the locomotor activity of the animals. The F-1983 dose that can raise hexobarbital-inhibited locomotor activity of mice by 200% is more than 10 times smaller than the dose required for nonpretreated animals. In the case of amphetamine, the two doses are not essentially different. In contrast to amphetamine, F-1983 has only slight circulatory, respiratory, and intestinal effects. In the EEG, F-1983, like amphetamine, causes flattening of cortical potentials, increased frequency, disappearance of sleep-spindles, and inhibition of recruiting cortical responses to medial thalamus stimulation. However, F-1983 acts on electrical brain function even after fairly small doses and, above all, the dose span between intensified cerebral activity and increased muscular activity is distinctly greater in F-1983 than in amphetamine. The site of attack of F-1983 lies, as with amphetamine, in the bulbo-mesencephalic reticular formation, as has been demonstrated electroencephalographically by section of the brainstem at different levels. The points of emphasis in the action of the two compounds are quite different.

Research Institute of Dr. S. Wauder
Bern, Switzerland

1819 Tyce, Gertrude & McGuckin, Warren F.
Urinary tryptamine excretion: Causes and significance. Journal of the American Medical Association, 183(8):818, 1963.

Questions are asked as to the significance of an elevated urinary tryptamine level and the effect of drugs and diet on that level. The reply states that an increase in tryptamine excretion is a sensitive indication of MAO inhibition. A number of

drugs interfere with the fluorescence of tryptamine, such as belladonna and opium. The isolated amine can be condensed with formaldehyde to form tetrahydronorharman and subsequently oxidized to norharman by H_2O_2 . The level of tryptamine can also be varied by the individual's diet, since it is found in ordinary fruits and vegetables. Tryptamine formation after a loading dose of tryptophan has been used as an index of decarboxylase inhibition by a number of hypotensive agents, for example, methyl dopa.

Rochester, Minnesota

1820 Pintilie, C., Mison-Crighel, N., & Crighel, E. *Activitatea glutaminazei I in focarul convulsiv produs prin mescalina. (Activity of glutaminase I in a convulsive focus evoked by mescaline.)* Studii si Cercetari de Neurologie, 8(2): 271-276, 1963.

An experimental study was performed on 15 cats, which were immobilized and kept under artificial respiration. Seven out of eight cats evidenced convulsive states in the right ectosylvian area upon application of a paper filter saturated with an aqueous 3% solution of mescaline hydrochloride. Changes were registered by electrocorticogram. Ten minutes after application, a 2-second complete convulsion was recorded in the mescaline-treated cats, always appearing in a portion of the right ectosylvianus. In the control group, convulsions appeared in the left ectosylvianus. This convulsive activity produced by mescaline in the cerebral cortex of the cat did not produce significant modifications of the activity of glutaminase I. Glutaminase I activity cannot be connected with an electric-convulsive activity but rather must be of a functional or irritative type.

Institute of Neurology
Academy of I.P. Pavlov, R.P.R.

1821 Carlsson, Arvid & Lindqvist, Margit. *Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain.* Acta Pharmacologica et Toxicologica 20(2):140-144, 1963.

White mice of either sex, weighing about 20 g, were injected i.p. with mialamide 100 mg/kg. After 1 hour, various doses of

chlorpromazine, haloperidol, phenoxybenzamine, or promethazine were given i.p. After another 3 hours, the animals were sacrificed. As controls, mice received nialamide alone. Brains of nine mice were pooled and homogenized with 18 ml 0.4 N perchloric acid. After centrifugation, 11 ml of the extract was taken for analysis of normetanephrine and 3-methoxytyramine. The remaining part of the extract (about 5 ml) was taken for assay of noradrenaline and dopamine. The accumulation in mouse brain of the catecholamine metabolites 3-methoxytyramine and normetanephrine brought about by inhibition of monoamine oxidase was found to be enhanced by small doses of chlorpromazine and haloperidol, but phenoxybenzamine and promethazine were ineffective. Hypothermia could be eliminated as a causative factor. It is suggested that the effect is due to a compensatory activation of monoaminergic neurons after blockade of monoaminergic receptors.

University of Göteborg
Göteborg, Sweden

1822 McLardy, Turner. *Amphetamine and ammonshorn-sclerosis.* Nature, 198 (4883):900, 1963.

A neurohistological survey was made of 11 guinea pigs (400 to 600 g in weight) in which 10 mg amphetamine was always injected i.m. 0.5 to 4 hours before exposures to carbon monoxide hypoxia; at the time of exposure, amphetamine was still producing motor activation (notably in the form of compulsive gnawing). Of five of these animals which had six, five, four, three, and three full seizures, respectively, only two displayed ischemia in the CA2 (pyramidal cells of the hippocampus), and then only in some mild degree. Acetazolamide, in lieu of amphetamine, in a similar smaller series of experiments, tended to suppress seizures but not to diminish CA2 pathology. In 11 control guinea pigs not premedicated with amphetamine, relatively selective CA2 ischemia of severe or moderate degree was present in 7 having at least three full seizures each; of mild degree in 2 having at least four full seizures each; and absent in 2 having only incomplete seizures with forelimbs and hindlimbs never running simultaneously. There is established clinical testimony for the paradoxical anti-stimulatory value of amphetamine in psychomotor problems related to epilepsy in childhood, as well as recent physiological experimental evidence that amphetamine may

increase midbrain inhibition of hippocampal neurones. It is suggested that hippocampal microelectrode experiments should be performed on the guinea pig rather than on the rat for more rapid and more effective results.

St. Andrew's Hospital
Northampton, England

1823 Busfield, D., Child, K. J., Atkinson, R. M., & Tomich, E. G. **An effect of phenobarbitone on blood-levels of griseofulvin in man.** *Lancet*, 2(7316):1042-1043, 1963.

The effects of phenobarbital on the blood levels of griseofulvin were studied in 8 men and 8 women. Four volunteers of each sex received 30 mg of phenobarbital on one evening and t.i.d. the following 2 days. Each of the 16 volunteers swallowed four 25-mg tablets of griseofulvin at 7:30 A.M. the morning after the last barbiturate dose. Blood samples were obtained by venepuncture 2, 4, 8, and 26 hours later. Volunteers were asked not to take other drugs or alcohol during the weekend, but no effort was made to control diet. Blood-levels of the antibiotic were measured by the spectrophotofluorometric method of Bedford, Child, and Tomich. The blood-antibiotic levels in the phenobarbital-treated group were lower than those in the control group. An analysis, in which the area of the curve relating blood-griseofulvin level to time for each volunteer was used as the response meter, indicated that the difference is statistically significant ($P < 0.05$).

Glaxo Research Ltd.
Greenford, Middlesex, England

1824 Calesnick, Benjamin. **Drug toxicity.** *Journal of the American Medical Association*, 184(11):903-904, 1963. (Letter).

In a comment on two reports of potentiation of organophosphorus poisoning by phenothiazines, pharmacological proof is given for the contraindication of these tranquilizers in such poisoning cases. Organic phosphorus compounds (including parathion,

sarin, isoflurophate, tetraethylpyrophosphate, hexaethylpyrophosphate, and octamethylpyrophosphoramide, inhibit cholinesterase. Acetylcholine is, therefore, free to induce its typical cholinergic effects, such as muscle tremor, fasciculation, muscular paralysis, and death from involvement of the respiratory muscles. In addition, bronchial constriction, bradycardia, and circulatory collapse may develop. Usually, when phenothiazines are administered intravenously or intramuscularly, there is a drop in blood pressure and tachycardia occurs. There is adequate justification for not using the phenothiazines as antidotes in phosphorus poisoning. The antidote of choice is atropine combined with an oxime compound. The oxime compounds are specific and capable of reversing the symptoms of excessive cholinesterase inhibition by reactivating the enzyme. Pyridine-2-aldoxime methyl chloride has been found to be extremely effective.

Philadelphia, Pennsylvania

1825 Oberman, Harvey, Buse, John, Herbert, Elmore G., Ellison, Haskell S., & Buse, Maria G. **Effect of chlordiazepoxide on thyroid function.** *Journal of the American Medical Association*, 184(4):342, 1963.

The effect of chlordiazepoxide on thyroid function was studied in healthy volunteers and patients. Serum-protein-bound iodine, triiodothyronine- I^{131} red-cell uptake, and 24-hour thyroidal I^{131} uptake were measured before treatment was given and on the last day of therapy. Chlordiazepoxide was administered orally in doses ranging from 10 to 20 mg q.i.d. The maximal dose range was maintained for a minimum of 10 days. Chlordiazepoxide caused no significant changes in any of the parameters of thyroid function studied.

55 Doughty Street
Charleston, South Carolina

1826 Raynor, Richard B. & McMurtry, James G. **Prevention of serotonin-produced cerebral vasospasm. An evaluation of blocking agents.** *Journal of Neurosurgery*, 20:94-96, 1963.

An evaluation of the blocking agents of serotonin-induced cerebral vasospasm was conducted using the middle cerebral artery

and surrounding cortex of 16 cats. One animal was administered reserpine (15 mg i.v.) 16 hours before the experiment. In another animal, 5 mg i.v. of reserpine was given simultaneously with the application of topical serotonin. Chlorpromazine (5 mg i.v.), 1-benzyl-2,5-dimethyl bufotein hydrochloride (BAB), 5 mg i.v. and intraarterial, 1-benzyl-2,5-dimethyl serotonin (BAS), 1 mg i.v., and isoxsuprine hydrochloride were administered to the animals to produce arterial spasms that lasted from 3 to 15 minutes. It was felt that any compound effective against serotonin-induced spasm should be able consistently to reverse the spasm in less than 5 minutes, or prevent it when used before the serotonin was applied. None of the compounds tested fulfilled these criteria. The BAB, BAS, chlorpromazine, and reserpine have proved to be effective anti-serotonic agents when tested in vitro or against the pressor effects of serotonin in vivo.

Columbia-Presbyterian Medical Center
New York, New York

- 1827 van der Schoot, Johan B., Creveling, Cyrus R., Nagatsu, Toshiharu, & Udenfriend, Sidney. On the mechanism of inhibition of dopamine- β -oxidase by benzyl-oxyamines. *Journal of Pharmacology and Experimental Therapeutics*, 141(1):74-78, 1963.

An attempt was made to elucidate the mechanism of the inhibition of dopamine- β -oxidase by benzyloxyamine derivatives. Benzyloxyamine derivatives have been shown to be inhibitors of the enzyme dopamine- β -oxidase by virtue of their isosteric relationship to the corresponding phenethylamine derivatives. Benzyloxyamine and two hydroxylated analogs were shown to inhibit the enzyme by a mechanism which is initially competitive with substrate. When preincubated with the enzyme, however, the compounds become so firmly bound that substrate cannot readily reverse the inhibition. Although preincubation results in a noncompetitive type of inhibition, the inhibitor-enzyme complex can, in many instances, be dissociated by prolonged dialysis.

National Heart Institute
Bethesda, Maryland

- 1828 Tuttle, Richard S. & Preston, James B. The effects of diphenylhydantoin (Dilantin) on segmental and suprasegmental facilitation and inhibition of segmental motoneurons in the cat. *Journal of Pharmacology and Experimental Therapeutics*, 141(1):84-91, 1963.

The influence of diphenylhydantoin was studied on certain neural pathways in both spinal-cat and "pyramidal-cat" preparations. Fifty adult cats were used in the experiments. Placement of tracheal and venous cannulae and insertion of an arterial cannula were performed on all animals under ether anesthesia. One group was rendered acutely spinal by spinal cord section and the brain destroyed by anemic decerebration. The second group was prepared as "pyramidal cats" in accordance with the procedure used by Preston and Whitlock (1960) on monkeys. Diphenylhydantoin was found to have no apparent effect on single-volley transmission through segmental monosynaptic reflex pathways, although the phenomenon of post-stimulation potentiation was depressed by the drug. In the spinal-cat preparation, spatial monosynaptic facilitation and "direct" inhibition were not altered by drug injection, but the pattern of sural nerve volleys on extensor monosynaptic reflexes was influenced by the drug. In the "pyramidal-cat" preparation, inhibition of segmental motoneurons initiated by either brain-stem reticular formation or motor-cortex stimulation was depressed by diphenylhydantoin. Brain-stem and motor-cortex facilitation of segmental motoneurons was augmented by drug injection. It is implied that diphenylhydantoin depresses interneuronal activity and has a generalized depressant influence on both suprasegmental facilitatory and inhibitory pathways, the latter being affected quantitatively to some extent.

State University of New York
Upstate Medical Center
Syracuse, New York

- 1829 Share, N. N. & Melville, K. I. Centrally mediated sympathetic cardiovascular responses induced by intraventricular norepinephrine. *Journal of Pharmacology and Experimental Therapeutics*, 141(1):15-21, 1963.

The cardiovascular changes induced by the intraventricular injection of norepinephrine, epinephrine, and 5HT were compared in

normal animals and in animals pretreated with intraventricular reserpine. In pentobarbitalized cats with artificial respiration, intraventricular injections of norepinephrine (40 µg and 80 µg) consistently led to sinus bradycardia (in significantly greater degree in nonvagotomized animals). Centrally reserpinized vagotomized cats, intraventricular injections of norepinephrine (40 µg and 80 µg) induced marked pressor responses, cardioacceleration, and, at times, slight electrocardiographi ischemic-like changes. Following central reserpinization, 1 hour after spinal-C2 section, the arterial blood pressure and heart rate were not reduced but showed a slight increase, and the cardiovascular responses following intraventricular injections of norepinephrine (40 µg and 80 µg) were significantly less than in nonspinal reserpinized animals. Intraventricular injections of epinephrine (40 µg) in centrally reserpinized cats induced significantly less pressor responses and cardioacceleration than did an equal amount of norepinephrine, but, after spinal-C2 section, cardiovascular responses were similar to those observed with norepinephrine after spinal section. Intraventricular injections of 5HT (80 µg) in centrally reserpinized cats induced only minor insignificant blood pressure and heart-rate variations. Norepinephrine might be of physiological importance as a transmitter substance in central sympathetic activation at the brainstem level, although high concentrations of it may depress central mechanisms.

Gill University
Montreal, Canada

30 Dobkin, Allen B., Israel, Jacob S., Byles, Peter H., & Lee, Peter K. Y. Chlorprothixene and amitriptyline: Interaction with thiopentone, circulatory effect and antisialogogue effect. British Journal Anaesthesia, 35:425-432, 1963.

A few of the pharmacological properties (interaction with thiopental, circulatory effect, and antisialogogue effect) of chlorprothixene and amitriptyline have been clearly defined. Crossover experiments were carried out four times at weekly intervals in 10 mongrel dogs (mean weight: 17.6 kg). Each dog received thiopental (20 mg/kg body weight) injected at the rate of 150 mg/minute, which was followed by 0.5 mg/kg of chlorprothixene or 5.0 mg/kg of amitriptyline. Both of the drugs prolonged anesthesia, but the sedative effect of amitriptyline

was considerably milder than that of chlorprothixene. Chlorprothixene at 1- to 3-day intervals was given to 12 healthy male human subjects (19 to 22 years of age, mean weight 165 pounds). In 10 of these subjects, the tests were repeated with chlorprothixene, and then with amitriptyline. The blood pressure and pulse rates in a supine position and a 60-degree head-up position were recorded before and after drug administration. Both drugs caused orthostatic hypotension in the tilt position. This effect was rather severe with chlorprothixene and mild with amitriptyline. In the same 10 male subjects, parotid salivary excretion was measured before and after i.v. injection of carbamylcholine chloride (0.12 mg) plus adrenaline (9.06 mg). These measurements were compared with those taken when chlorprothixene (10 mg i.v.) was given 10 minutes before the mixture. The drug had no effect on the secretion of saliva from the parotid duct either before or after stimulation with the carbamylcholine--adrenaline mixture, although it is reported to exert very strong anticholinergic effects on other organ systems.

State University of New York
Upstate Medical Center
Syracuse 10, New York

1831 Tesařová, O., Molčan, J., & Jenča, G. Zmeny hepatickej funkcie v priebehu liečby chlorprothixenom. (Changes in the liver function during chlorprothixene therapy.) Activitas Nervosa Superior, 5: 204, 1963.

A total of 572 hepatic tests were made in 17 psychiatric patients with various psychoses during a course of treatment with chlorprothixene (average dose 250 mg/day p.o., and 125 mg/day by injection). Hepatic tests were done at least every 14 days during the 6-week course of treatment. The following laboratory tests were performed: (1) erythrocyte sedimentation; (2) paper electrophoresis of serum protein; (3) thymol test; (4) Takata-Ara reaction; (5) cadmium rapid test; (6) photometric determination of bilirubin; (7) serum refraction; (8) King--Armstrong determination of alkaline phosphatase; (9) serum transaminase; (10) the prothrombin speed test of Quick; and (11) the Rosenthal and White bromsulfalein test. The greatest change was evident in the thymol test, which in 29% of the cases was at the upper limit of the normal range, and in individual cases reached the edge of the pathological range. The cadmium reaction

became more positive in three cases, and a pathological value was obtained for bilirubin in one case. Alkaline phosphatase values showed a ten-fold increase, with a tendency toward fast normalization. Serum transaminase values were more positive in a few cases, which later normalized. The bromsulfalein-retention test gave varied results. According to the present study, chlorprothixene has no hepatotoxic effect in most cases. It may cause a slight change in liver function within normal limits. Although in individual cases it gave pathological results for hepatic tests, these were reversible.

Charles University
Bratislava, Czechoslovakia

1832 Mišurec, J. & Náhunek, K. **Fotometrazolový práh při léčbě některými antidepresivy.** (Photometrazol threshold in the course of therapy with some antidepressive drugs.) *Activitas Nervosa Superior*, 5:181-182, 1963.

The photometrazol threshold, as a measure of brain excitability, was investigated in 14 patients receiving treatment with imipramine, 7 patients receiving prothiadene, and 8 patients under treatment with propazepine. In all, there were 12 men and 17 women, with an age range of 20 to 67 years. Their diagnoses were: endogenous depression in 21, reactive depression in 4, depressive neurasthenia in 1, schizophrenia in 2, and psychogenic psychosis in 1. Equal doses of the three drugs were administered. The initial dose of 75 mg p.o. was increased by 25 mg on successive days, so that dosage reached 300 mg/day on the tenth day. The results were expressed as percentage reduction of the photometrazol threshold, compared to values obtained before administration of the drugs. The Wilcoxon statistical test showed that the threshold increase was significant at the 1% level for imipramine and at the 5% level for prothiadene, and was insignificant in the case of propazepine. In the course of the threshold test, two patients treated with imipramine exhibited grand mal seizures at a dosage of 500 mg, and, in one case, high-voltage delta activity of an episodal character appeared.

Medical Faculty
Brno, Czechoslovakia

1833 Nickel, J., Breyer, U., Claver, B., & Quadbeck, G. **Zur Wirkung von Aminoethanol-Derivaten auf das Zentralnervensystem.** (On the effect of aminoethanol derivatives on the central nervous system.) *Arzneimittel-Forschung*, 13:881-883, 1963.

In studying the effect of aminoethanol derivatives on the CNS, four experiments were made. (1) Passage of the blood--brain barrier by C^{14} labeled glucose was studied in mice pretreated with 100 mg/kg dimethylaminoethanol (deanol), 46 mg/kg procaine, or 20, 50, and 75 mg/kg centrophenoxine i.p. (2) The radioactivity of the blood, cerebrum, cerebellum, and brain stem was determined in Wistar rats pretreated with 50 mg/kg centrophenoxine i.p. and injected with Na^{24+} and with $HP^{32}O_4$. (3) The influence of 50 mg/kg centrophenoxine on the passage of acridin orange (40 mg/kg, i.p.) from the blood to the brain was studied in Wistar rats. (4) Rats of the strain of the Max Planck Institute for Medical Research were implanted with bilateral frontal and occipital cortical electrodes, and the EEG was recorded with the rats kept in a pressure chamber at nominal altitudes of 7,000 m and of 8,700 m for 5-minute periods. The results showed that deanol has no influence on the passage of glucose from the blood to the brain of the mouse. Procaine clearly reduced the uptake of glucose by the brain. Centrophenoxine, however, produced a definite increase in the passage of glucose across the blood--brain barrier. Because neither phosphate uptake nor acridin orange values changed, it may be concluded that the increase in uptake produced by centrophenoxine cannot be attributed to a general increase in permeability of the blood--brain barrier. The high-altitude EEG showed that centrophenoxine clearly increases the altitude resistance of the brain.

University of Homburg
Homburg/Saar, Germany

1834 Crandell, D. LeRoy, Fox, J. W. C., & Siewers, Ralph deS. **Failure to replenish catecholamine stores in reserpinized dogs.** *Journal of Anesthesiology*, 24(5): 636-639, 1963.

The ephedrine response test (E.R.T.) was used in 20 reserpinized, anesthetized dogs to determine the time taken to restore reserpine-depleted adrenergic response with

ad without dopamine and norepinephrine infusions. In the E.R.T., changes in pulse rate and arterial pressure are monitored after the i.v. administration of 15 mg of ephedrine sulfate. Catecholamines were depleted by i.m. reserpine, 0.1 mg/kg daily for 3 days. The ephedrine response was regained in a mean time of 9.3 days after reserpine. Neither 10-mg dopamine infusions nor 1-mg norepinephrine infusions increased recovery time. The E.R.T. may have considerable clinical value in measuring the rate of catecholamine biosynthesis.

Woman Gray School of Medicine
 Winston-Salem, North Carolina

335 Bertler, A., Gottfries, C. G.,
 Nordenfelt, I., & Rosengren, E.
monoamine levels and choline acetylase activity in brain and effect of reserpine and dihydroxyphenylalanine after cerebral lesions. *Medicina Experimentalis*, 9:17-19, 1963.

The effects of reserpine and DOPA in the brain after destruction of the various parts of the cerebrum were studied in rats and dogs. The effect on the choline acetylase activities and the noradrenaline and dopamine concentrations in different parts of the brain was also studied after complete destruction of some cerebral structures. Bilateral removal of the cerebral cortex in the rabbit did not have any influence on the effect of reserpine (1 mg/kg body weight). The rabbits became less active and were almost somnolent after 30 minutes. The time course and the degree of the reaction to reserpine were the same as those seen in the sham-operated controls. Rabbits in which the caudate nuclei had been removed bilaterally did not show any detectable difference in their reaction to reserpine, as compared to controls. Destruction of the cerebral cortex in dogs and rabbits or the thalamus in rabbits did not produce any significant changes in the concentration of dopamine and the choline acetylase activity in the caudate nucleus.

Universities of Gothenburg and Lund
 Lund, Sweden

336 Anichkov, S. V. & Zavodskaya, I. S.
Action of neurotropic drugs on reflex gastric wall dystrophy. *Medicina Experimentalis*, 8:296-306, 1963.

To study the action of neurotropic drugs on reflex gastric wall dystrophy, rats were injected i.p. with the tropine ester of

benzilic acid, 3 mg/kg; the dimethylaminoethyl ester of benzilic acid, 3 mg/kg; and benactyzine, 3 mg/kg. The first two drugs used on rats after the infliction of duodenum trauma proved effective in preventing gastric mucosa dystrophy. Benactyzine proved to be equally effective in preventing gastric mucosa dystrophy caused by electric stimulation of immobilized animals. In experiments with meprobamate (50 mg/kg), the reflex gastric dystrophy caused either by trauma of the duodenum or by electrical stimulation was intensified. For ascertaining dystrophy in stages preceding microscopic alterations, the rate of methionine incorporation into the mucosa, submucous, and muscular tissues of the gastric wall of guinea pigs was determined by the specific radioactivity of the tissue proteins and by means of autoradiography of histological slices. Sodium amytal (100 mg/kg) and phenobarbital (100 mg/kg) were also effective in preventing reflex dystrophy.

Institute of Experimental Medicine
 Leningrad, U.S.S.R.

1837 Takesada, Masashi, Kakimoto, Yasuo,
 Sano, Isamu, & Kaneko, Ziro. **3,4-Dimethoxyphenylethylamine and other amines in the urine of schizophrenic patients.** *Nature*, 199(4889):203-204, 1963.

An improved method was devised for obtaining chromatograms of urinary amines. An amount of urine containing 50 mg creatinine was acidified to pH 2 by addition of concentrated hydrochloric acid and heated in boiling water for 30 minutes. Initial purification of the amines was carried out with a modification of the method used by Kakimoto and Armstrong (1962) for the purification of urinary phenolic amines. The compounds were visualized with ninhydrin reagent. Recovery of authentic 3,4-dimethoxyphenylethylamine added to urine using the procedure was about 90%. Resolution of the amines on the chromatogram was satisfactory. Urine specimens were obtained from 78 schizophrenic patients, 16 of whom were under treatment with psychotropic drugs (usually chlorpromazine), 21 psycho-neurotic patients, and 46 normal subjects. Frequency of the appearance of 3,4-dimethoxyphenylethylamine is higher in urine of schizophrenics than in normal subjects. The amount in the urine of two normal subjects did not increase after oral administration of 0.5 g of 3,4-dihydroxy-L-phenylalanine,

and the amine could not be detected in the urine of two patients with pheochromocytoma. In urine of three groups of 5 rats, each given i.m. injections of 3,4-hydroxy-L-phenylalanine (100 mg/kg), dopamine (10 mg/kg), and norepinephrine (1 mg/kg), respectively, 3,4-dimethoxyphenylethylamine could not be detected. Results suggest that 3,4-dimethoxyphenylethylamine originates from dietary sources or is a product formed by intestinal bacteria. The occurrence of other urinary amines seen in the chromatograms is discussed.

Osaka University Medical School
Osaka, Japan

- 1838 Llaurodo, Josep G. The cation-retaining action of sympathomimetic substances in the rat. *Chemotherapy*, 6: 363-381, 1963.

The effects of amphetamine and related substances and a variety of sympathomimetic substances unrelated to amphetamine on water, sodium, and potassium excretion were studied in intact and adrenalectomized rats. Test compounds were given orally and subcutaneously. Results for all compounds are tabulated as urine output in ml, urine sodium ion and potassium ion contents in microequivalents, and cation-retaining index (C.-R.I.), which is defined in the text. Many of the sympathomimetic substances produced water, sodium, and potassium retention in both intact and adrenalectomized animals, with the latter showing greater retention. Subcutaneous administration produced greater retention than oral administration. For materials studied in a wide dose range, there was a linear log dose--response relationship when the excreted amounts of sodium and potassium were plotted in terms of the C.-R.I. In contrast to the other substances studied, L-epinephrine increased urine output, especially at the smallest doses tested, while causing retention of sodium and potassium. No evidence was found for the proposed diuretic effect of *d*-amphetamine. A structure--activity relationship was shown to exist for the effects on the C.-R.I.; the active chemical substituents known to increase pressor responses also increased cation-retaining activity.

The Graduate Hospital
University of Pennsylvania
Philadelphia, Pennsylvania

- 1839 Kuntzman, Ronald & Jacobson, Martin M. Monoamine oxidase inhibition by a series of compounds structurally related to bretylium and guanethidine. *Journal of Pharmacology and Experimental Therapeutics*, 141(2):166-172, 1963.

The effect of some benzyl and phenethylguanidines on MAO activity was studied in vitro and in vivo. These guanidines were found to be competitive and reversible inhibitors of MAO. *N*-*O*-Chlorobenzyl-*N'*,*N''*-dimethylguanidine sulfate (B.W.392C60) was as potent an MAO inhibitor in vitro as phenylisopropylhydrazine (PIH), while its dechlorinated congener *N*-benzyl-*N'*,*N''*-dimethylguanidine sulfate (bethanidine) showed little activity. The presence of a halogen in the ortho position of the benzene ring greatly enhanced enzyme inhibition, whereas substituents placed elsewhere on the phenyl moiety resulted in a decreased inhibition. Bethanidine, for example, is about 100 times less active in vitro and at least 15 times less active in vivo than B.W.392C60. Bethanidine and B.W.392C60, in addition to inhibiting MAO, also inhibit the physiological release of norepinephrine at sympathetic nerve endings and block its release when produced by guanethidine administration. Studies that showed that B.W.392C60 is a much more potent MAO inhibitor in vitro and in vivo than bethanidine also suggested that the blockade of the sympathetic nervous system elicited by these drugs is not related to their ability to inhibit MAO activity.

Burroughs Wellcome & Company, Inc.
Tuckahoe, New York

- 1840 Kim, K. S. & Shore, P. A. Mechanism of action of reserpine and insulin on gastric amines and gastric acid secretion, and the effect of monoamine oxidase inhibition. *Journal of Pharmacology and Experimental Therapeutics*, 141(3):321-325, 1963.

The effects of reserpine and insulin on histamine and serotonin stores in the stomach and on the production of gastric acid are described, and the mechanisms of these effects are examined. The influence of MAO inhibition on reserpine and insulin is reported. Female Holtzman rats (150 to 200 g) were given 5 mg/kg reserpine i.p. or 5 U/100 g insulin i.p. Certain rats were

agotomized, others were given the ganglion blocking agent chlorisondamine (5 mg/kg) or the MAO inhibitor pheniprazine (PIH) (5 mg/kg). Reserpine and insulin provoked gastric-acid secretion and produced gastric lesions. Both agents lowered stomach histamine content, but reserpine also lowered serotonin content. Gastric acid secretion, lesions, and histamine lowering produced by either agent were greatly inhibited or blocked by vagotomy. A small part of reserpine-induced effects was mediated by ganglionic stimulation. The PIH inhibited reserpine-induced gastric acid secretion, serotonin lowering, and lesion formation but did not alter the histamine-lowering action of reserpine. The PIH had no effect on insulin-induced lesions, acid secretion, or histamine lowering. It is concluded that both reserpine and insulin cause gastric histamine release by central vagal stimulation, leading, in turn, to gastric acid secretion. It is further concluded that PIH protects against reserpine-induced responses by a local action, possibly due to the presence of a high free-serotonin concentration.

The University of Texas
Southwestern Medical School
Dallas, Texas

1841 Varma, D. R. & Benfey, B. G.
Antagonism of reserpine-induced
subsensitivity to tyramine by methyldopa.
Journal of Pharmacology and Experimental
Therapeutics, 141(3):310-313, 1963.

The effect of reserpine on tyramine response was studied in anesthetized cats injected i.p. with reserpine (1 mg/kg) the day before the experiment. Other drugs injected i.p. 1 or 2 days prior to the experiment included α -methyldopa, bretylium tosylate, guanethidine, chlorpromazine HCl, and nialamide. The cardiovascular actions of tyramine in spinal cats and its inotropic action on the rat isolated papillary muscle were tested following methyldopa, reserpine, and reserpine injected after methyldopa. It was found that reserpine reduced the pressor and inotropic effects of tyramine and stellate ganglion stimulation in spinal cats and the inotropic action of tyramine and butyrylcholine on the papillary muscle, whereas methyldopa did not inhibit these responses. However, in cats pretreated with methyldopa, reserpine did not reduce the actions of tyramine. Because the

effects of stellate ganglion stimulation and butyrylcholine were inhibited when reserpine had been injected after methyldopa, it is concluded that methyldopa did not interfere with the release of endogenous catecholamine by reserpine. On the basis of these results, the cause of the subsensitivity to tyramine following reserpine is suggested to be an antagonism between reserpine and tyramine at the receptor level.

McGill University
Montreal, Canada

1842 Peterson, Ruth D., Beatty, Clarissa H., & West, Edward S. The effects of tranquilizing drugs on muscle metabolism. Journal of Neuropsychiatry, 5(1):86-91, 1963.

Adductor muscle fibers from female, Sprague-Dawley depancreatized and control rats (180 to 220 g in weight) were incubated with tranquilizers, and the tranquilizing effects on lactate and pyruvate production, amino acid nitrogen release, adenosine triphosphate and adenosine diphosphate (ATP + ADP) and creatine phosphate (CrP) concentrations were determined by assay techniques. Final drug concentrations in the incubation flasks were 2.6×10^{-5} M, 1.3×10^{-4} M, and 2.6×10^{-4} M for chlorpromazine and thioridazine, and twice these amounts for amphenidone. Lactate production was unaffected by chlorpromazine or thioridazine in fibers from diabetic rats. Whereas pyruvate production was decreased, amino acid release was increased, and ATP + ADP and CrP decreased. In control rat fibers, chlorpromazine had the same effects, whereas in concentrations up to 5.4×10^{-4} M, amphenidone had none of these effects. These results show that the phenothiazine tranquilizers can interfere with the maintenance of energy in skeletal muscle fibers.

Tulane University Medical School
New Orleans, Louisiana

1843 Condouris, George A. Conduction block by cocaine in sodium-depleted nerves with activity maintained by lithium, hydrazinium or guanidinium ions. Journal of Pharmacology and Experimental Therapeutics, 141(2):253-259, 1963.

The depressant action of cocaine was investigated in sodium-deficient from peripheral nerves in which excitability was artificially

maintained by the sodium substitutes lithium, hydrazinium, or guanidinium ions. The action of cocaine was quantitatively affected by the nature of the sodium substitute. The effect of cocaine was greater in guanidine-supported nerves and hydrazine-supported nerves than in nerves maintained by sodium or lithium. A mutual antagonism was demonstrated between cocaine and each of the substitutes. The cocaine-sensitive excitability mechanism, which in normal nerves is associated with sodium, was not circumvented through the use of substitute cations. Instead, the cocaine--sodium antagonism is replaced by a cocaine--sodium-substitute antagonism, emphasizing the competitive mechanism as the cause of local nerve block by cocaine.

Seton Hall College of Medicine and Dentistry
Jersey City, New Jersey

1844 Goldberg, M. E., Johnson, H. E., Knaak, J. B., & Smyth, H. F., Jr. Psychopharmacological effects of reversible cholinesterase inhibition induced by *N*-methyl 3-isopropyl phenyl carbamate (Compound 10854). *Journal of Pharmacology and Experimental Therapeutics*, 141(2):244-252, 1963.

N-Methyl-3-isopropylphenyl carbamate (Compound 10854) was studied for its psychopharmacological and acetylcholinesterase inhibitory effects. The following experimental animals were used: male and female rats, 175 to 225 g in weight, aged 50 to 75 days; male rats, 350 to 450 g in weight, aged 125 to 150 days; and female mice, 19 to 24 g in weight. Male rats were three to four times as sensitive as females to the lethal and effective dose on avoidance behavior; in both cases a comparison of the LD₅₀ with the ED₅₀ revealed about a 25-fold factor. Atropine sulfate inhibited the effects of Compound 10854 on both avoidance and escape behavior, while methyl atropine blocked only the inhibitory effects on escape behavior. Dose--response studies, utilizing dust inhalation techniques, for behavioral and anticholinesterase effects, indicated that threshold effects on discrete avoidance studies are associated with about a 50% inhibition of total brain cholinesterase. A linear decrease on avoidance efficiency was obtained when brain enzyme activity was decreased from 50% to 25% of normal. Peak effect on behavior and brain cholinesterase occurred at 30 minutes following i.p. administration of Compound

10854. Inhibitory effects were of short duration, avoidance performance was normal after 75 minutes, and enzyme activity was within control limits by 180 minutes after injection. Studies on forced and spontaneous motor activity indicated that the carbamate elicited activity patterns similar to chlorpromazine. Barbiturate potentiation was blocked only by pretreatment with atropine sulfate, which alone significantly reduced barbiturate sleeping time. Potentiation also occurred when the carbamate was given 24 hours prior to the barbiturate. It is concluded that behavioral changes induced by Compound 10854, but not barbiturate potentiation, are mediated by central anticholinesterase effects.

Mellon Institute
Pittsburgh, Pennsylvania

1845 Stone, Clement A., Stavorski, John M., Ludden, Carl T., Wenger, Herbert C., Ross, Charles A., Totaro, James A., & Porter, Curt C. Comparison of some pharmacologic effects of certain 6-substituted dopamine derivatives with reserpine, guanethidine and metaraminol. *Journal of Pharmacology and Experimental Therapeutics*, 142(2):147-156, 1963.

Because tissue catecholamine depletion induced by reserpine and guanethidine is associated with adrenergic neurone blockade and differential sympathomimetic amine antagonism, catecholamine depletion by 6-substituted dopamine derivatives was studied to see if similar associated effects occurred. The effects of the derivatives were compared with the effects of metaraminol. Pretreatment of dogs with 6-hydroxydopamine, 6-aminodopamine, and α -methyl-6-hydroxydopamine 16 to 24 hours before experimentation caused a reduction or blockade of the pressor effects resulting from stimulation of the central ends of the vagus nerves and from injection of amphetamine and phenethylamine. Norepinephrine pressor responses were not reduced at the same time. As with reserpine and guanethidine, these delayed actions were associated with an ability to deplete the catecholamines from the heart. 6-Hydroxydopamine was able to block the cardioacceleration due to postganglionic fiber stimulation of the dog's heart. 6-Aminodopamine reduced the catecholamine content of cardiovascular structures but not other tissues, whereas reserpine reduced the level in these tissues, as well as in cardiovascular structures.

the additional property of the 6-substituted opamines, shared with reserpine, was an ability to augment pressor responses of phenethylamine in the dog within minutes of administration. That their prominent sympathomimetic-like cardiovascular actions in the dog may not be primarily responsible in producing the reserpine-like actions was indicated by the failure of metaraminol and epinephrine to produce similar actions, although metaraminol proved to be a potent releaser of catecholamines in the heart of the dog.

Merck Institute for Therapeutic Research
West Point, Pennsylvania

846 Kirpekar, S. M., Cervoni, Peter, & Couri, Daniel. **Depletion and recovery of catecholamines and adenosine triphosphate of rat adrenal medulla after reserpine treatment.** *Journal of Pharmacology and Experimental Therapeutics*, 142(1):71-75, 1963.

The effect of reserpine on the catecholamine and adenosine triphosphate contents of the adrenal medullae of albino, Wistar rats (200 to 250 g in weight) was studied. Reserpine (10 mg/kg i.p.) reduced epinephrine, norepinephrine, and adenosine triphosphate levels by about 90% to 95% within 4 hours. Recovery of amines and adenosine triphosphate was studied at intervals up to 14 days following reserpine. Recovery of norepinephrine was slightly faster than epinephrine, and almost complete replacement occurred in about 7 days. Epinephrine recovery was complete in 2 weeks. Recovery of adenosine triphosphate followed the same time course as the recovery of total catecholamines, and 50% replacement of both took place in 4 days following reserpine injection. Pheniprazine, when administered to cats 2 mg/kg per day for 7 days, had no effect on medullary amines.

Downstate Medical Center
Brooklyn, New York

847 Kirpekar, S. M. & Cervoni, Peter. **Effect of cocaine, phenoxybenzamine and phentolamine on the catecholamine output from spleen and adrenal medulla.** *Journal of Pharmacology and Experimental Therapeutics*, 142(1):59-70, 1963.

To determine whether nerve terminals and/or receptors play any significant role in affecting levels of neurally released transmitter substance in venous effluents, the

effects of cocaine, phenoxybenzamine, and phentolamine on the catecholamine output from the spleen and the adrenal medulla were studied. Splenic nerves were stimulated at frequencies of 10/second and 30/second for a total of 200 stimuli, and blood samples from splenic vein were assayed for norepinephrine. At 10/second, the amount of norepinephrine was 0.25 ng/stimulus, while at 30/second, the output was 0.67 ng/stimulus. Cocaine caused only a slight increase of norepinephrine output at lower frequency, while at higher frequency the pattern of output remained the same. Phenoxybenzamine and phentolamine increased the transmitter output at lower frequency by about five times and outputs at lower and higher frequencies were nearly equal. Phenoxybenzamine also caused increase in the background pressor activity of plasma samples. The splanchnic nerve to the adrenal medulla was stimulated at frequencies of 2/second, 5/second, 10/second, 20/second, and 30/second for a total of 300 stimuli. Cocaine and phentolamine had no effect; phenoxybenzamine increased the background pressor activity markedly and enhanced the catecholamine output. Cocaine potentiates the submaximal contractions of the nictitating membrane of the cat induced by stimulation of the postganglionic fibers of the superior cervical ganglion. Phenoxybenzamine potentiates the relaxation of the colon in response to submaximal stimulation of the lumbar colonic nerves more effectively than cocaine. It would seem that adrenergic alpha-receptors are involved in the activation of the neurally released transmitter from spleen.

State University of New York
Downstate Medical Center
Brooklyn, New York

1848 Joglekar, G. V., Chitale, G. K., & Balwani, J. H. **Protection by indigenous drugs against hepatotoxic effects of carbon tetrachloride in mice.** *Acta Pharmacologica et Toxicologica*, 20:73-79, 1963.

The protection offered by promethazine, chlorpromazine, and LIV 52 (an indigenous Indian proprietary medicine) against the hepatotoxic effects of carbon tetrachloride was investigated in a 72-hour study and a 21-day study. For the short-term study, 50 male albino mice (25 to 40 g) were divided into five equal groups. One group received no treatment and four groups received 0.1 ml of carbon tetrachloride intragastrically.

Three of these four groups received promethazine (1 mg/mouse), chlorpromazine (0.4 mg/mouse), or LIV 52 (25 mg/mouse) immediately after and again 4 hours after carbon tetrachloride. The other group received no protective agent. In the long-term study, distribution into groups and the doses of drugs were the same as in the short-term study. Carbon tetrachloride was given five times at 3-day intervals. The livers of those dying during both studies and those surviving to the end were examined histologically. In the carbon tetrachloride control groups of both studies, active necrosis and early cirrhotic changes were observed. In the LIV 52 groups, these histological changes were prevented, but promethazine and chlorpromazine showed no protection against carbon tetrachloride.

B. J. Medical School
Poona 1, India

- 1849 Lightowler, J. E. & Smith, A. E. Wilder. β -(*N*-Pyrrolidyl)-butyroanilid (W.S.10). Its sub-acute toxicity, influence on morphine analgesia in the rat and morphine analgesia and respiratory depression in the rabbit. Archives Internationales de Pharmacodynamie et de Therapie, 144(1-2):97-111, 1963.

The compound β -(*N*-pyrrolidyl)-butyroanilid (W.S.10) was investigated in four experiments to determine subacute toxicity, morphine-analgesia potentiation, and respiratory-depressant properties. Forty male and 40 female rats were randomly assigned to various concentrations of W.S.10 in their drinking water. The concentration giving 50% mortality was 1.28 g/100 ml solution, females being more susceptible than males. In studies of analgesia potentiation in rats, 50 mg/kg of W.S.10 i.p. potentiated the analgesic effects of morphine hydrochloride, codeine phosphate, dihydrocodeine acid tartrate, pethidine hydrochloride, and propoxyphene hydrochloride. In the rabbit, 20 mg/kg W.S.10 i.v. potentiated morphine analgesia. W.S.10 did not, however, potentiate morphine respiratory depression in rabbits when the drugs were administered i.v. in varying doses. Thus, by using morphine in the presence of W.S.10, the analgesia obtained could be increased about six times for a given degree of respiratory depression.

Edinburgh Pharmaceutical Industries, Ltd.
Edinburgh 11, Scotland

- 1850 Schaper, Wolfgang K. A., Jageneau, Anton H. M., & Bogaard, Johannes M. Hemodynamic and respiratory responses to dehydrobenzperidol, a potent neuroleptic compound in intact anesthetized dogs. Arzneimittel-Forschung, 13:316-317, 1963.

Mongrel dogs weighing between 19 and 42 kg, unselected as to age and sex, were anesthetized and catheters were introduced into the right atrium, the right heart chamber, the left ventricle, and the femoral artery. Dehydrobenzperidol, a potent neuroleptic agent, was then infused at constant rates (0.01 mg per minute over a period of 100 minutes; then 0.1 mg per minute over 100 minutes). This was followed by a post-drug period during which only the solvent was infused at 1 ml per minute. Dehydrobenzperidol caused a marked increase in peripheral blood flow, a moderate increase in cardiac output and heart rate, and a small decrease in pulse pressure. Central venous pressure and mean circulatory-transit time decreased. An increase in effective ventilation was one of the earliest signs of the drug action. Renal hemodynamics and renal excretory functions were not altered significantly, except for increase in chloride excretion.

Research Laboratories of Dr. C. Janssen
Beerse, Belgium

- 1851 Vidal-Beretervide, K. & Monti, M. Pharmacological study of tropyl-chromone-2-carboxylate and some of its derivatives. Arzneimittel-Forschung, 13: 452-454, 1963.

The pharmacologic action of tropyl-chromone-2-carboxylate hydrochloride was studied in pigeons (290 to 300 g), mice (18 to 22 g), rats (150 to 250 g), rabbits (1,800 to 2,500 g), cats (2,800 to 3,500 g), and dogs (4 to 15 kg) in an attempt to explore the possibility of reinforcing the depressor or antitremor action of the compound. Tropyl-chromone-2-carboxylate hydrochloride and its quaternary derivatives, tropyl-chromone-2-carboxylate methobromide and tropyl-chromone-2-carboxylate methiodide, were injected, according to the various species, i.m. (dosage not given), i.v. (1 to 5 mg/kg), i.p. (30 to 50 mg/kg), and intracisternal (5 mg). It was concluded that tropyl-chromone-2-carboxylate hydrochloride possesses a very distinct stimulating action upon the CNS, as reflected by its convulsant action and by its antagonistic action on respiratory depression.

in conjunction with morphine. Quaternary compounds had a pronounced ganglioplegic action, moderate curare-like action, and at large doses, convulsant action more distinctly observable when injected intracisternally. One of the compounds studied exhibited propine-like or adrenolytic peripheral action.

Faculty of Medicine
Montevideo, Uruguay

52 Sigg, E. B., Osborne, M., & Korol, B. **Cardiovascular effects of imipramine.** *Journal of Pharmacology and Experimental Therapeutics*, 141(2):237-243, 1963.

An analysis of the cardiovascular effects of imipramine in anesthetized and unanesthetized dogs (10 to 18 kg) and a comparison of these effects with those of phenothiazines were presented. The EEG measurements were made 0.5, 1, 2, 4, 24, and 48 hours after a single injection of imipramine (0.32, 1.0, and 3.0 mg/kg i.v. at 1-week intervals). From experiments conducted, the following cardiovascular effects of imipramine were observed: (1) It lowered the blood pressure in anesthetized dogs in doses from 1 to 8 mg/kg, i.v. However, in anesthetized renal hypertensive dogs, single i.v. injections (0.32 to 3 mg/kg) of imipramine did not exert an antihypertensive effect. (2) Myocardial contractility and heart rate were increased by low doses (20 µg i.v.) and were decreased by higher doses (2 to 5 mg/kg i.v.) of imipramine. (3) Coronary blood flow was increased after intrarterial injection of small doses (5 µg to 10 µg), not changed after i.v. doses of 10 µg/kg to 320 µg/kg, and decreased after i.v. administration of 2 to 5 mg/kg. It was concluded that cardiovascular reflex functions are impaired by a blockade of pressoreceptor mechanisms due to the local anesthetic effect of imipramine.

Biological Research Laboratories
Roseland, New York

53 Anderson, Edmund G. & Ammann, Arthur. **The effects of monoamine oxidase inhibitors on neuromyal transmission.** *Journal of Pharmacology and Experimental Therapeutics*, 140(2):179-182, 1963.

A study of the neuromyal activity of representative MAO inhibitors was undertaken to

help delineate their actions. The MAO inhibitors tranlycypromine, phenylisopropylhydrazine, N-methyl-N-benzyl-2-propynylamine (MO 911), ethyltryptamine, harmaline, amphetamine, and methamphetamine all produced a reversible block of neuromyal transmission in the isolated rat phrenic-nerve--diaphragm preparation. They did not block when application was restricted to the nerve, and they increased the force of contraction of directly stimulated muscle. They did block the action of acetylcholine on the denervated diaphragm. It is concluded that these compounds block transmission by a mechanism not involving inhibition of monoamine oxidase.

Seton Hall College of Medicine and Dentistry
Jersey City, New Jersey

1854 Brodey, James F., Steiner, William G., & Himwich, Harold E. **An electrographic study of psilocin and 4-methyl- α -methyl tryptamine (MP-809).** *Journal of Pharmacology and Experimental Therapeutics*, 140(1):8-18, 1963.

An electroencephalographic analysis of psilocybin, psilocin, 4-methyl- α -methyl tryptamine (MP-809), 4-hydroxy- α -methyl tryptamine (MP-14), and 1-methyl psilocybin was made to determine their sites of action. Fifty-nine albino rabbits (2.3 to 2.8 kg) were used in the experiments. Four different preparations were employed, two involving transection of the brain and one of the cervical cord. In experiments on the intact brain, groups of six rabbits were used, and each of the five compounds was tested. The precollicular, prepontine preparation was employed in 10 rabbits to localize sites of action of MP-809 and psilocin. In other experiments involving the postcollicular, postpontine transection, 15 animals were studied for additional information on the same two drugs. In addition, four animals having a transection at the level of the first cervical vertebra were used in a further study of psilocin. In rabbits with intact brain, all five drugs produced EEG alert patterns. In the precollicular-prepontine-preparation animals, MP-809 produced only a slight lowering of amplitude in the EEG pattern. When one-third the dose of eserine needed to evoke sustained activation in an animal so transected was administered to animals pretreated with MP-809, a fully alert pattern was obtained indicating a site of minor action rostral to the midbrain and probably cholinergic in nature. When MP-809 was

administered to animals transected in a postcollicular, postpontine plane, the EEG pattern duplicated, with minor variations, the EEG arousal seen in intact animals. Thus a potent site of action for MP-809 was found in the midbrain, a region possessing a strong adrenergic component. Psilocin failed to evoke alert patterns in animals transected either rostral or caudal to the midbrain, which excludes the midbrain and structures more rostrally situated as possible sites of action. Animals injected with psilocin and subsequently transected at the level of the first cervical vertebra continued to display EEG alerting, indicating a site of action below the midbrain but excluding the spinal cord.

Galesburg State Research Hospital
Galesburg, Illinois

stimulation of the adrenal medulla. A contributing factor in the origin of hypotension following MAO inhibition may be interference with catecholamine release.

Medical College of South Carolina
Charleston, South Carolina

See also: 1632, 1687, 1689, 1770, 1771, 1772, 1775, 1784, 1793, 1794, 1795, 1797, 1798, 1799, 1804, 1806, 1807, 1857, 1860, 1861, 1862, 1863, 1864, 1865, 1866, 1867, 1871, 1872, 1874, 1877, 1879, 1881

1855 Gatgounis, John & Aycock, John.
Effects of monoamine oxidase inhibitors on adrenal medullary responses to nicotine and tetramethylammonium. Journal of Pharmacology and Experimental Therapeutics, 141(1):50-57, 1963.

These experiments were designed to determine the responsiveness of the adrenal medulla to the chromaffin-cell stimulants, nicotine and tetramethylammonium, following the intra-aortic administration of a series of MAO inhibitors. Injection of the MAO inhibitors 1-(*p*-dimethylaminobenzyl)-2-(5-methyl-3-isoazoylcarbonyl) hydrazine (RO 5-1025), β -phenylisopropylhydrazine (JB 516), nialamide, iproniazid, isocarboxazid, and the non-MAO inhibitor isoniazid in the following respective doses produced increments in heart contractile force in dogs anesthetized with a mixture of pentobarbital sodium and barbitol sodium: 60 mg/kg, 15 mg/kg, 60 mg/kg, 100 mg/kg, 50 mg/kg, and 175 mg/kg. Similar injections of iproniazid and nialamide decreased arterial blood pressure, whereas RO 5-1025, JB 516, and isocarboxazid increased arterial blood pressure. Decreased cardiac responsiveness to norepinephrine (1 μ g/kg) injections were produced by nialamide (100 mg/kg), iproniazid (200 mg/kg), and isocarboxazid (100 mg/kg). Adrenal medullary responsiveness to nicotine (5 μ g/kg i.v.) and tetramethylammonium (30 μ g/kg i.v.) was significantly blocked by pretreatment with the MAO inhibitors. Pretreatment with isoniazid (175 mg/kg) and a vehicle did not interfere with chemical

BIOCHEMISTRY

356 Ross, S. B. **In vivo inactivation of catecholamines in mice.** *Acta Pharmacologica et Toxicologica*, 20(3):267-273, 1963.

Three experiments were performed to help elucidate the pathway for the biological inactivation of catecholamines: (1) the effect of catechol-*O*-methyl transferase (COMT) inhibitors and MAO inhibitors on catecholamine-induced tachycardia in mice; (2) the influence of catecholamines on the uptake of tritiated noradrenaline in vitro; and (3) the substrate specificity of isoproterenol to MAO compared to that of noradrenaline and adrenaline. Adrenaline, noradrenaline, and isoproterenol were given i.v. in experiments with mice; the MAO inhibitor pheniprazine and the COMT inhibitor progallol were given i.p. The duration of the tachycardiac effect of isoproterenol in mice was considerably prolonged when COMT was inhibited, but was much less affected by MAO inhibition. The effects of adrenaline and noradrenaline were only slightly prolonged by either COMT inhibition or MAO inhibition alone. When both enzymes were inhibited simultaneously, the durations of tachycardia induced by adrenaline and noradrenaline were still much less than that of tachycardia induced by isoproterenol when COMT alone was inhibited. Isoproterenol did not block the uptake of tritiated noradrenaline by heart tissues in vitro at concentrations 10 to 100 times greater than effective concentrations of adrenaline and noradrenaline. The importance of uptake and binding of the naturally occurring catecholamines as the first inactivation reaction, and the differences in this respect between these amines and isoproterenol are discussed.

3 ASTRA
Ödertälje, Sweden

357 Melmon, Kenneth & Sjoerdsma, Albert. **Serotonin in Platelets. Its uptake and disappearance after administration of the amine by mouth.** *Lancet*, 2(7303):316-18, 1963.

A study was conducted to determine if changes in blood-serotonin levels develop

during repeated administration of the amine. The subjects used were 4 male and 3 female, normal volunteers, (aged 19 to 22) and a 50-year-old male patient with severe Lemec's cirrhosis. Each subject ingested a diet without fruits or fruit juices and with a constant protein content. In preliminary observations, 3 of the volunteers were given capsules containing 10 mg of serotonin base (as the creatinine sulfate) p.o. every 6 hours for 5 days, and the recovery as urinary 5HTAA was compared with that during the ingestion of a similar amount of serotonin in bananas over another 5-day period. Serotonin creatinine sulfate was given orally in capsules 6-hourly to a maximal daily dosage of 160 mg base for at least 18 days before, during, and after which chemical studies were done. Results reported were obtained in 4 of the normal subjects and in the patient with cirrhosis. All blood samples were obtained when the patients were fasting; when they were ingesting serotonin, blood samples were drawn just before administration of an amine dose. Increases in platelet serotonin of 2-1/2 to 6 times were observed. When the 5HT was discontinued, platelet serotonin decreased with an average half-life of 3 days. These findings may be relevant to endomyocardial fibrosis in Uganda.

National Heart Institute
Bethesda, Maryland

1858 Baštecký, J., Laurentová, J., & Zaplatílková, H. **Rychlá metoda na průkaz Guajacuranu v moči. (Rapid method of determination of guaiacuran (guaiacol glycerin ether) in urine.)** *Activitas Nervosa Superior*, 5:223-224, 1963.

The authors describe a method for the determination of guaiacuran in the urine, based on four qualitative reactions. After ether extraction of alkaline urine and desiccation of the ether extract, the procedure consists essentially of the following: (1) addition of concentrated sulfuric acid, giving a carmine-red reaction; (2) addition

of Marquise reagent, giving a violet color; (3) addition of hydroquinone giving a reddish fluorescence; and (4) addition of a mixture of potassium ferrocyanide and ferric chloride giving a pale blue color. Although the reaction with potassium ferrocyanide and ferric chloride is nonspecific, there is no nonspecific negative reaction. The entire test takes 10 minutes. Standard guaiacuran solution gave a similar reaction to that of the urine, indicating that guaiacuran was not metabolized. Guaiacuran may be demonstrated in the urine 30 minutes after its administration. This qualitative method may be used in the diagnosis of acute poisoning and for control of medication in psychiatric institutions.

Charles University
Prague, Czechoslovakia

- 1859 Posner, Herbert S., Culpan, Roger, & Levine, Jerome. **Quantification and probable structure, in human urine, of the nonphenolic and phenolic metabolites of chlorpromazine.** *Journal of Pharmacology and Experimental Therapeutics*, 141(3):377-391, 1963.

Two methods for the estimation of urinary chlorpromazine metabolites are described: (1) a quantitative paper chromatographic method, which is satisfactory for the routine estimation of the large number of metabolites; and (2) a methyl orange color reaction, which is satisfactory for grouped metabolites. Eight 24-hour urines and an incomplete 24-hour specimen from patients receiving chlorpromazine chronically were analyzed. Comparison was made with urine obtained from two individuals receiving a single dose and six controls receiving none. The nonphenolic metabolites included unchanged chlorpromazine, chlorpromazine-*N*-oxide, chlorpromazine sulfoxide, and the mono- and di-*N*-demethylated sulfoxides. The latter were predominant. Monophenolic metabolites included a chlorpromazine monophenol, its mono- and di-*N*-demethylated derivatives, and a neutral compound. Phenolic metabolites predominated over nonphenolic by about 2:1 or 3:1. A di-oxygenated metabolite is present, which was extractable primarily into butanol after hydrolysis with β -glucuronidase. Urine of two individuals receiving a single dose of chlorpromazine contained predominantly the nonphenolic metabolites. A significant trend toward decreased percent recovery of metabolites in the urine with increasing drug dosage was noted. There was no

correlation, under conditions of chronic drug administration, between the ratio of phenolic to nonphenolic metabolites and drug dose. The 3-hydroxypromazine was shown to be a metabolite of promazine. Qualitatively, at least, the metabolism of promazine was similar to that of chlorpromazine.

St. Elizabeths Hospital
Washington, D.C.

- 1860 Kirshner, Norman, Rorie, Mary, & Kamin, Dorothy L. **Inhibition of dopamine uptake in vitro by reserpine administered in vivo.** *Journal of Pharmacology and Experimental Therapeutics*, 141(3):285-289, 1963.

To determine whether reserpine administered in vivo can inhibit the uptake of catecholamines, the accumulation of dopamine- C^{14} and its conversion to norephrine was measured in adrenal gland homogenates of 29 control cats and 28 cats injected with reserpine (2.5 mg i.p.). It was observed that up to 2 days after the injection of reserpine, the total catecholamine content of the adrenal gland was 70% depleted and its ability to accumulate dopamine was inhibited by about 90%. By the third day, the catecholamine content and the ability to accumulate and convert dopamine to norepinephrine began to recover and at the end of 2 weeks were at normal levels. These observations are interpreted to support the hypothesis that reserpine causes a depletion of the catecholamine stores by inhibiting the transport of dopamine into the chromaffin granules and there it is subsequently converted to norepinephrine.

Dale University Medical Center
Durham, North Carolina

- 1861 Kaplan, Meta, Gitlow, Stanley, & Smith, Alfred A. **Metabolism of Δ^1 -norepinephrine-7- H^3 in rabbits tolerant to Δ^1 -norepinephrine.** *Journal of Pharmacology and Experimental Therapeutics*, 142(3):306-311, 1963.

To investigate the possibility of a relationship between the inactivation rate of norepinephrine in the rabbit and tolerance to this compound, female albino rabbits (1.6 to 2.0 kg in weight) made tolerant to

narcotic and lethal doses of *l*-norepinephrine (3.2 mg/kg i.v.) were infused with *dl*-norepinephrine- H^3 at a rate of 50 μ c/kg min⁻¹ for 20 minutes. Concentration of norepinephrine- H^3 in plasma obtained during infusion and for 40 minutes thereafter were similar for the tolerant group, controls, and a group treated 24 hours earlier with reserpine (1 mg/kg). Except for reduced concentrations in the heart, uptake of norepinephrine- H^3 in organs of tolerant animals was similar to controls. In the groups treated with reserpine, norepinephrine- H^3 binding was less in all organs but the kidney. Only about half the normal catechol concentrations were found in hearts of tolerant animals, yet both spleen and kidney were found to contain several times the control amount. Although reserpine markedly diminished the catechol content of the heart, no significant decrease occurred in spleen or kidney. Mean concentrations of unchanged norepinephrine- H^3 in the urines of each group were similar, although significantly less normethanephrene was found in the urines of tolerant animals, as well as higher concentrations of unknown catabolites. Altered peripheral metabolism does not appear to be related to the development of tolerance to the lethal and narcotic effects of norepinephrine.

New York University Medical Center
New York, New York

362 Hug, C. C., Jr. & Woods, L. A.

Tritium-labeled nalorphine: Its CNS distribution and biological fate in dogs.
Journal of Pharmacology and Experimental Therapeutics, 142(2):248-256, 1963.

The purpose of this investigation is to extend, by means of radiochemical techniques, earlier observations on the tissue distribution and metabolic fate of nalorphine. The preparation of tritium-labeled nalorphine (nalorphine- H^3) and procedures for analysis of this material and its metabolites in biological specimens are described. Following subcutaneous administration of nalorphine- H^3 (2 mg/kg) to dogs, plasma levels and urinary excretion of the free and conjugated drug were determined. Nalorphine- H^3 was rapidly conjugated in the dog, and a glucuronide conjugate represented the major excretion product of the drug. Excretion of free and conjugated nalorphine- H^3 in the urine accounted for 80% to 90% of the administered dose. The levels of free nalorphine- H^3 in selected areas of the CNS after 2 mg/kg s.c. rose very rapidly to a

concentration approximately 5 times greater than the simultaneous concentration of free nalorphine- H^3 in plasma. The time-concentration curves for the free drug in plasma and in the CNS appear to correlate with the magnitude of the pharmacological effects of nalorphine observed in the intact animal. Differences in concentration of the narcotic antagonist in various areas of the CNS have been attributed to differences in blood supply to those areas and to a differential affinity of gray and of white CNS tissue for the compound.

University of Michigan Medical School
Ann Arbor, Michigan

1863 Harrison, William H., Levitt, Morton, & Udenfriend, Sidney. **Norepinephrine synthesis and release in vivo mediated by 3,4-dihydroxyphenethylamine.** *Journal of Pharmacology and Experimental Therapeutics*, 142(2):157-162, 1963.

The effect of dopamine (3,4-dihydroxyphenethylamine) on the synthesis and release of norepinephrine was studied in the heart of male, albino guinea pigs (200 to 250 g). Dopamine (50 mg/kg i.p.) was an effective norepinephrine releasing agent and synthesis stimulator. The lowest levels of norepinephrine were obtained between 30 and 60 minutes after administration of dopamine but returned to control levels within 8 hours. Within 1 hour, administration of dopamine- C^{14} (35 mg/kg i.p.) produced 31% the total norepinephrine found in the heart. At 3 hours it was 37% and at 8 hours it was 44%. Dopamine- C^{14} , administered to animals pretreated 16 hours before with Aramine (10 mg/kg) or α -methyl-*m*-tyramine (100 mg/kg), synthesized the same amounts of norepinephrine as without these releasing agents. Pretreatment with MAO inhibitor, isopropyl-nicotinyl hydrazine (100 mg/kg i.p. and 50 mg/kg 14 hours later) 1 hour before dopamine (100 mg/kg), caused increased dopamine effects on norepinephrine due to the MAO inhibitor making more dopamine available to the tissues. These results explain how dopamine can cause norepinephrine release without effecting a net change in tissue norepinephrine levels.

National Institutes of Health
Bethesda, Maryland

- 1864 Horita, A. The influence of drug-tissue interactions on the inhibition of monoamine oxidase by pheniprazine and iproniazid. *Journal of Pharmacology and Experimental Therapeutics*, 142(2):141-146, 1963.

The MAO inhibiting properties of pheniprazine (PIH) and iproniazid were investigated in vivo and in vitro. In the in vitro experiments, it was shown that PIH disappeared rapidly from the supernatant fluid of brain homogenate. This effect was apparently nonenzymic for boiled brain homogenate was even more active in inactivating PIH. Liver tissue was also effective but to a lesser degree. Disappearance of active PIH from the supernatant correlated well with the rapid onset of peak inhibition produced by this compound. Iproniazid disappearance was not evident with low concentrations of tissues, but with larger amounts of liver homogenate an early loss of MAO inhibitory activity was seen in the supernatant fraction, followed by a sudden increase in inhibitor activity. Concomitant assay of the enzyme indicated a progressively increasing inhibition of the MAO reaching maximum after 2 hours of preincubation with the inhibitor. The supernatant MAO inhibitory activity of brain and liver homogenates prepared from rats pretreated with PIH disappeared rapidly and, within 60 minutes, detectable amounts were essentially absent. In iproniazid-pretreated animals, supernatant MAO inhibitory activity persisted for 12 to 18 hours after drug administration, although peak levels occurred some 1 to 2 hours after injection.

University of Washington
School of Medicine
Seattle, Washington

- 1865 Dubnick, Bernard, Leeson, Gerald A., Leverett, Ruth, Morgan, D. Fay, & Phillips, G. E. Sympathomimetic properties of chlorphentermine: Metabolism, metabolic effects, interaction with reserpine and biogenic amines. *Journal of Pharmacology and Experimental Therapeutics*, 140(1):85-92, 1963.

The biochemical properties of chlorphentermine (*L*-chloro- α , α -dimethylphenethylamine) as a member of the class of sympathomimetic amines were studied. The effect of an i.v. dose of chlorphentermine (3.2 mg/kg) on glucose and free fatty acids (FFA) in plasma was studied in male mongrel dogs. The drug raised FFA levels but not glucose levels.

Chlorphentermine in doses up to 36 mg/kg i.v. failed to realert mice treated with reserpine (10 mg/kg i.p.), but administration of 16 mg/kg i.p. phenelzine (MAO inhibitor) followed by chlorphentermine (15 to 20 mg/kg i.v.) caused intense motor stimulation for more than 5 hours. Determination of norepinephrine levels in tissues (brain, heart, fat, spleen) of several species (male Sprague-Dawley rats, 250 to 350 g; Manor Swiss MF-1 female mice, 18 to 25 g; and female guinea pigs, 250 to 400 g) treated with 25 mg/kg i.v., 15 mg/kg i.v., and 40 mg/kg i.v. chlorphentermine, respectively, did not provide clear evidence that CNS, adipose tissue, or cardiovascular effects of this compound are mediated by catecholamine release. Reserpine (10 mg/kg i.p.) depleted the brain serotonin, but not norepinephrine in mice. Phenelzine (16 mg/kg i.p.) plus a second dose of reserpine (10 mg/kg i.p.) failed to alter their depressed status but caused an additional release of norepinephrine. Comparison of rates of metabolism and lipid-aqueous distribution ratios of chlorphentermine and several closely related compounds suggested that the prolonged pharmacological effects of chlorphentermine may be attributable to the influence of the *L*-chlorine.

Warner-Lambert Research Institute
Morris Plains, New Jersey

- 1866 Axelrod, Julius & Inscoe, Joseph K. The uptake and binding of circulating serotonin and the effect of drugs. *Journal of Pharmacology and Experimental Therapeutics*, 141(2):161-165, 1963.

A method for the estimation of C^{14} -serotonin uptake, distribution, and disappearance from tissues is described, and the effect of various drugs on these processes is reported. Adult, male mice weighing 25 g were injected i.v. with 25 g of C^{14} -serotonin, and adult, male rats weighing 150 to 200 g were injected i.v. with 250 μ g of C^{14} -serotonin. For studying the distribution of radioactive serotonin in tissues, pooled organs from three mice and the organs of a single rat were used for assay. Isoamyl alcohol extracts from whole mice and organ tissues obtained at various time intervals up to 1 week after injections of serotonin were evaporated in vacuo and taken up in ethanol for assay of specificity. Reserpine and JB 516 (β -phenylisopropylhydrazine) were given i.p. 2 hours before i.v. injection of C^{14} -serotonin; all other drugs were given i.p. 10 minutes before i.v. C^{14} -serotonin. In

the whole mouse, about half the circulating serotonin was rapidly bound in tissues and slowly released over many days. It is proposed that binding might serve as a major mechanism for the inactivation of circulating serotonin. The C^{14} -serotonin is unequally taken up in the various tissues examined. It is selectively taken up and retained by the lung, spleen, and adrenal gland. Tryptamine, reserpine, and imipramine increase the rate of destruction of circulating serotonin, but chlorpromazine, tyramine, amphetamine, cocaine, LSD, and guanethidine have no effect. The MAO inhibitor JB 516 slows its disappearance. Tryptamine, reserpine, cocaine, imipramine, and LSD blocked the uptake of serotonin in the lung and spleen, but chlorpromazine had no significant effect.

National Institutes of Health
Bethesda, Maryland

1867 Potter, Lincoln T. & Axelrod, Julius. **Studies on the storage of norepinephrine and the effect of drugs.** *Journal of Pharmacology and Experimental Therapeutics*, 140(2):199-206, 1963.

A series of sympathomimetic amines was tested for ability to deplete endogenous and radioactive norepinephrine from the rat heart. Tyramine was found to release H^3 -norepinephrine that has been recently bound to a greater degree than H^3 -norepinephrine that has been present in the heart for a longer period of time. The specific activity of depleted norepinephrine is different from that of the amine that remains in the heart. The tyramine-releasable store was calculated to have a half-life of several hours, while the tyramine-resistant store had a half-life of about 1 day. Contrastingly, the specific activity of norepinephrine depleted by reserpine is the same as that which remains in the heart. The MAO inhibitor JB-516 (β -phenylisopropylhydrazine) partially blocked depletion of norepinephrine by reserpine, guanethidine, and α -methyl-*m*-tyrosine, but not the release by amphetamine. These results support the concept that reserpine and guanethidine release norepinephrine, which is largely metabolized intraneuronally by monoamine oxidase, whereas sympathomimetic amines act upon another store to release norepinephrine from the nerve metabolized by catechol-O-methyl transferase. Bretium was found to block partially the depleting actions of reserpine and guanethidine, but not the

release by amphetamine or α -methyl-*m*-tyrosine. Cocaine blocked norepinephrine depletion by tyramine.

National Institute of Mental Health
Bethesda, Maryland

1868 Bacon, Gordon. **Ultraviolet spectrophotometric analysis of barbiturates.** *Lancet*, 1(7288):1000-1001, 1963. (Letter).

The successful use of Broughton's technique for the spectroscopic identification of barbiturates is reported in reply to a report of failure with the method. The ultraviolet absorption spectra of blood extracts in two cases of Tuinal overdosage corresponded to the spectrum obtained from the contents of a capsule of the drug (2.5 μ g per ml each of amylobarbitol and quinalbarbitol). The spectrum obtained from the contents of a capsule of Amesec (amylobarbitol, 1.6 μ g per ml; aminophylline 8.4 μ g per ml) showed isobestic points which would lead to the presence of a barbiturate being suspected. Only two specimens containing bemegride in addition to barbiturate were examined; in both instances, the characteristic features appeared upon re-examination of the spectra after the alkaline extraction had been allowed to stand, the distortion at the shorter wavelengths disappearing as the unstable bemegride decomposed. Distorted spectra will be obtained if interfering substances are present (especially in extracts of gastric contents and urine) but, after careful inspection of such spectra, the presence of a barbiturate can be suspected.

Dorset County Laboratory
Dorchester, Dorset, England

1869 George, William H. S. & Matthews, A. A. **Barbiturates giving atypical results on ultraviolet spectrophotometric analysis.** *Lancet*, 1(7286):890-891, 1963. (Letter).

Comment is made on an ultraviolet spectrophotometric method employed for estimating barbiturates in blood, gastric washings, and urine. The caustic and borate absorption spectra of the blood, gastric washings, and urine of patients who had taken tablets identified as phenobarbital, amylobarbitol,

sodium amytal, quinalbarbital, or pentobarbital corresponded to the spectra obtained from individual tablets of these barbiturates and fulfilled the criteria necessary for the identification of barbiturates. It was suggested that bemegride in blood may hide the presence of barbiturates by raising the caustic component, although there is always a difference in extinction between the caustic and borate curves at 260 μ . In a patient who had taken 1-bromo-1-ethylbutyrylurea and pentobarbital, the absorption spectra were normal, with the caustic component raised above the borate. This abnormality seemed to be due to either 1-bromo-1-ethylbutyrylurea or a filter in the tablet.

Derbyshire Royal Infirmary
Derbyshire, England

- 1870 Broughton, P. M. G. Barbiturates giving atypical results on ultra-violet spectrophotometric analysis. *Lancet*, 1(7293):1266-1267, 1963. (Letter: comment on letter by George and Matthews.).

The author comments on a letter (April 20 issue) that reported results obtained using paper chromatographic methods in detecting barbiturates in the presence of other drugs (see abstract 1869). The absorption spectra obtained were not characteristic of barbiturates, but were sufficiently abnormal to indicate that some other compound was present. Interference by bemegride was suspected when the sodium hydroxide extract showed a disproportionately high extinction at wavelengths below 240 $m\mu$. Bemegride decomposes rapidly and may be completely destroyed by incubation at 38° C for 2 hours. Alkaline solutions of carbromal also absorb at wavelengths below 250 $m\mu$, and decompose rapidly at pH 13. This interference may be found during gastric analysis in patients with carbromal--pentobarbital poisoning, but may be overcome by alkaline hydrolysis of the carbromal.

St. John's Hospital
Chelmsford, England

- 1871 Nikodijevic, Branislav, Creveling, Cyrus R., & Udenfriend, Sidney.
Inhibition of dopamine- β -oxidase in vivo by benzyloxyamine and benzylhydrazine analogs. *Journal of Pharmacology and Experimental Therapeutics*, 140(2):224-228, 1963.

A procedure is described for evaluating the effect of dopamine- β -oxidase inhibitors in

vivo, and investigations were conducted to determine whether enzyme inhibition, per se, can lead to depletion of norepinephrine in sympathetically innervated tissues. Albino male and female guinea pigs weighing from 230 to 260 g were used in the experiments. Drugs used and administered i.p. were: benzyloxyamine, benzylhydrazine, 3-hydroxy-4-bromo-benzyloxyamine (NSD-1055), aramine, α -methyl dopa hydrazine, 1-(5,6-dimethoxy-2-methylindole)ethyl-4-phenylpiperazine (Win-18501), and dopamine-1-C¹⁴. Norepinephrine was assayed by a modification of the fluorimetric trihydroxyindole procedure. Dopamine was assayed fluorimetrically. Norepinephrine was detected on paper chromatograms by spraying reference standards with 0.05 M potassium ferricyanide dissolved in 0.1 M phosphate buffer pH 7. Samples were dissolved in a solvent fluorophor mixture and radioactivity measured in a scintillation counter. Where aramine was used to deplete norepinephrine, the animals were pretreated with 10 mg/kg of aramine i.p. 15 to 18 hours prior to the experiment. In evaluating the effects of dopamine- β -oxidase inhibitors in vivo, it is concluded that benzyloxyamine and some ring substituted analogs were effective, but only one of these agents, the compound NSD-1055, produced even measurable effects on endogenous norepinephrine levels in guinea-pig tissues.

National Heart Institute
Bethesda, Maryland

- 1872 Kopin, Irwin J. & Gordon, Edna K.
Metabolism of administered and drug-released norepinephrine-7- H^3 in the rat. *Journal of Pharmacology and Experimental Therapeutics*, 140(2):207-216, 1963.

The possibility of differentiating between the metabolism of norepinephrine-7- H^3 that is circulating and norepinephrine-7- H^3 that is bound was investigated. The subjects were male Sprague--Dawley rats weighing 250 to 300 b. The rate of urine production under induced constant diuresis approximated the infusion rate (10 ml/hour) and facilitated timed urine collections. Four types of experiments were conducted: (1) *dl*-Norepinephrine (100 μ c in 2 ml saline) was administered i.v. (2) Pheniprazine (10 mg/kg) was administered i.p. 6 hours after norepinephrine (100 μ c i.v.) followed by reserpine (2.5 mg/kg i.p.) 10 hours after

the norepinephrine. (3) The following drugs were given at various times after the administration of the norepinephrine (100 µc i.v.): tyramine, reserpine, pheniprazine, empidine, guanethidine, 1,1-dimethyl-4-phenylpiperazinium (DMPP), α-methyldopa, tropine, and acetylcholine. All drugs were administered i.v. with the exceptions of reserpine and pheniprazine, which were administered i.p. Dosages, time intervals, and the percent of change in metabolites for these drugs are tabulated. (4) Pheniprazine (10 mg/kg) was administered i.p. and after 4 hours reserpine (2.5 mg/kg) was administered i.p. followed immediately by the norepinephrine (1.0 µc i.v.). Results indicate that the norepinephrine that is circulating and is being rapidly metabolized is preferentially O-methylated, while the bound norepinephrine is mostly deaminated. The administration of reserpine to rats that have been pretreated with an MAO inhibitor results in the discharge of a major portion of the released norepinephrine into systemic circulation in an active form. Acetylcholine and DMPP, like tyramine, release active norepinephrine into the circulation. The guanidine and phenylalanine drugs caused deamination.

National Institute of Mental Health
Bethesda, Maryland

1873 Curry, A. S. **Rapid method of screening for barbiturates.** British Medical Journal, 2(5364):1040-1041, 1963.

A method for screening 2 ml of blood for barbiturate in 5 minutes is described. The procedure is founded on the observation that barbiturates form mercury salts that are soluble in chloroform and insoluble in water. The extraction of the barbiturate from the blood into chloroform, the reaction with mercuric ions, and the color tests with dithizone for any mercury barbiturate in the chloroform are all performed in a 100-ml beaker. Extraction of the barbiturate from the buffered blood is performed by magnetic stirring using only 0.5 ml of chloroform. If a water-operated magnetic stirrer is used, the apparatus can be made portable, dependent only on a water supply. The only other equipment needed is a suction device. Concentrations and volumes of reagents are chosen to give a sensitive reaction to barbiturate levels in blood of 1 mg/100 ml or higher. Positive results will be obtained on blood from epileptics who may have normal phenobarbital levels of 5 mg/100 ml or from patients on

long-term barbitol therapy, who also may have levels of this order. Otherwise, normal therapeutic blood levels do not approach 1 mg/100 ml, and a positive reaction will indicate barbiturate poisoning as a cause of coma of undetermined origin. Results of a series of cases are given for the following barbiturates: amylobarbitol, abutobarbitol and pentobarbitol mixture, quinalbarbitol, aquinalbarbitol, and cyclo-barbitol mixture, pentobarbitol, and an amylobarbitol, butobarbitol, and quinalbarbitol mixture.

Home Office Forensic Science Laboratory
Harrogate, England

1874 Cucinell, S. A., Koster, R., Conney, A. H., & Burns, J. J. **Stimulatory effect of phenobarbital on the metabolism of diphenylhydantoin.** Journal of Pharmacology and Experimental Therapeutics, 141(2): 157-160, 1963.

A study was presented to determine if the chronic administration of phenobarbital can speed up the metabolism of diphenylhydantoin. Diphenylhydantoin (50 mg/kg i.v.) was administered to adult mongrel dogs by gelatin capsules. In male mice (20 to 22 g in weight), the drug (12 mg/kg) was administered by stomach tube. The elimination of the protective effects of diphenylhydantoin on maximal electroshock in mice pretreated with phenobarbital (100 mg/kg/day), phetharbitol (100 mg/kg/day), or chlorcyclizine (40 mg/kg/day) was discussed. In addition to the stimulatory effect of these drugs on diphenylhydantoin metabolism, they also stimulated the metabolism of phenylbutazone, administered i.p. as a 1.25% solution of its sodium salt, in the dog; phenylbutazone also contributed to its own metabolism.

The Wellcome Research Laboratories
Tuckahoe, New York

1875 Welles, J. S., McMahon, R. E. & Doran, W. J. **The metabolism and excretion of methohexital in the rat and dog.** Journal of Pharmacology and Experimental Therapeutics, 139(2):166-171, 1963.

The metabolism and excretion of methohexital, an ultrashortacting barbiturate, was studied in rats and dogs. Methohexital-C¹⁴ was

given i.v. in a dose of 10 mg/kg to both rats and dogs. Metabolites were measured in urine, feces, and respired air. Methohexital was metabolized in the dog and rat to 1-methyl-5-allyl-5-(1-methyl-4-hydroxy-2-pentynyl) barbituric acid. This involved hydroxylation of the penultimate carbon of a side chain, as has been observed in the metabolism of several other barbiturates. Demethylation of the *N*-methyl group was of minor importance. In a 7-hour period after intravenous administration of *N*-methyl-labeled methohexital, only 0.5% and 1.4% of the radioactivity was recovered as $C^{14}O_2$ in the expired air of the rat and dog, respectively. Excretion of metabolites was very rapid. After 1 hour the bile of the rat contained 50% of the intravenous dose. Total fecal excretion of the metabolites was 82.7%. The dog excreted, by both urinary and biliary routes combined, 21.7% of the dose in the first hour and 52.4% in 8 hours. Total fecal excretion in a dog was 30.1%.

Eli Lilly and Company
Indianapolis, Indiana

1876 Cochin, Joseph & Daly, John W. The use of thin-layer chromatography for the analysis of drugs. Isolation and identification of barbiturates and non-barbiturate hypnotics from urine, blood and tissues. *Journal of Pharmacology and Experimental Therapeutics*, 139(2):154-159, 1963.

An adaptation of thin-layer chromatography for the isolation and identification of a number of the commercially available barbiturates and nonbarbiturate hypnotics is described. The method is rapid, inexpensive, and simple. The hypnotics are extracted directly from urine, blood, or tissue homogenate, without prior precipitation of proteins, into methylene chloride at pH 5.0. After evaporation of the extracting solvent, the drugs are taken up in a small volume of ethanol and spotted on thin-layer chromatoplates. The *R_f* values for 16 barbiturates and 4 nonbarbiturate hypnotics in three solvent systems are given. Some examples of the metabolism of several of the barbiturates and non-barbiturate hypnotics after their administration to humans are described in order to show the usefulness of thin-layer chromatography in metabolic studies as well as in the fields of toxicology and forensic medicine. In the course of these studies of the practical applicability of these

techniques, a metabolite of secobarbital, 5-allyl-5-(1-hydroxy-1-methylbutyl) barbituric acid was isolated. This compound had been previously isolated from dog urine after administration of secobarbital, but had not been isolated from human urine. In a note to the paper, it is stated that further examination of urine extracts from patients receiving secobarbital revealed at least three other metabolites.

National Institutes of Health
Bethesda, Maryland

1877 Porter, Curt C. & Titus, David C. Distribution and metabolism of methyl-dopa in the rat. *Journal of Pharmacology and Experimental Therapeutics*, 139(1):77-87, 1963.

The tissue distribution and metabolism of methyl-dopa-1- C^{14} were studied in male albino rats (70 to 80 g). Methyl-dopa was widely distributed among the tissues examined (kidneys, lungs, plasma, heart, muscle, red cells, brain, liver, and spleen), but was markedly concentrated by the kidneys. Rapid expiration of $C^{14}O_2$ following administration of carboxyl- C^{14} -methyl-dopa showed decarboxylation to be an important metabolic reaction of the compound. The nature of urinary metabolites proved that not only decarboxylation but also O-methylation and oxidative amine deamination are major metabolic processes in the rats. The following metabolites of methyl-dopa were isolated in rat urine: methyl-dopa, α -methyl-dopamine, m-O-methyl-methyl-dopa, m-O-methyl- α -methyl-dopamine, 3-methoxy-4-hydroxyphenyl acetone, 3,4-dihydroxyphenyl acetone, conjugates of amines, and some unidentified substances. Methyl-dopa and small amounts of α -methyl-dopamine were found in the brains of mice and rats 1 hour after i.p. injection of the amino acid.

Merck Institute for Therapeutic Research
West Point, Pennsylvania

1878 Guzak, Regina & Caraway, Wendell T. Simultaneous determination of serum barbiturate and salicylate by ultraviolet absorption spectrophotometry. *American Journal of Medical Technology*, 29:231-239, 1963.

An ultraviolet spectrophotometric procedure is described for the simultaneous determination of barbiturates and salicylates in

blood serum. A correction factor to be applied to barbiturate values in the presence of salicylate was derived. Both compounds are extracted into chloroform with the aid of anhydrous sodium sulfate in an acid medium, then back extracted into borate buffer at pH 10. Barbiturate is determined from absorbance values at 239 m μ before and after acidification. Salicylate is determined from absorbance values at 280, 300, and 320 m μ after acidification. Interference by salicylate in the barbiturate determination is eliminated by applying the derived correction factor. Recovery of either compound from serum ranged from 95% to 99%. Attempts to apply the method to whole blood were unsatisfactory.

McLaren General Hospital
 Flint, Michigan

subjected to the tryptamine--tetrazolium method. In the white matter the myelin sheaths and the straight fibers traversing the granular layer showed a positive reaction for the monoamine oxidase. In the granular layer, a positive reaction was given by the glomeruli and the straight fibers. In comparison, the Purkinje cells gave a fainter reaction than the white matter or granular layer. Inhibition experiments, carried out by means of 1-isonicotinyl-2-isopropyl hydrazine and incubation, confirmed the specificity of the MAO reaction among the various elements by the absence of the positive reaction in the same elements.

Emory University
 Atlanta, Georgia

1879 Weiss, Benjamin & Rossi, G. Victor.
 Catecholamines. Biosynthesis and inhibitors of formation. *American Journal of Pharmacology*, 135:206-218, 1963.

In a brief review of the literature, the normal mechanisms involved in catecholamine formation and the drug-induced inhibition of catecholamine biosynthesis were discussed. A summary of the principal stages in the formation of the catecholamines, phenylalanine, tyrosine, DOPA, dopamine, 4-dihydroxy phenylacetic acid, norepinephrine, and epinephrine, was presented. DOPA-decarboxylase inhibition and dopamine- α -oxidase inhibition were discussed in view of a new approach to the treatment of hypertension.

Philadelphia College of Pharmacy and Science
 Philadelphia, Pennsylvania

1880 Tewari, H. B. & Bourne, G. H.
 Histochemical studies on the distribution of monoamine oxidase in the cerebellum of rat. *Acta Anatomica*, 52:334-340, 1963.

The detailed histochemical distribution of monoamine oxidase in the various constituents of the different cerebellar layers of unanesthetized rats is described. The cerebellum of healthy rats was removed and

1881 Fleming, W. W. A comparative study of supersensitivity to norepinephrine and acetylcholine produced by denervation, and decentralization and reserpine. *Journal of Pharmacology and Experimental Therapeutics*, 141(2):173-179, 1963.

The maximum supersensitivity produced by chronic treatment with reserpine was determined and used to quantitatively compare the effects of reserpine, decentralization, and denervation on the sensitivity of the cat nictitating membrane to norepinephrine and acetylcholine. Cats (2 to 4 kg body weight) of either sex were used for the experiment. The responses of the nictitating membrane were recorded with a Grass strain gauge and polygraph. Denervation was accomplished by removal of the right superior cervical ganglion and decentralization by the excision of about 2 cm of the right cervical sympathetic nerve. The optimum schedule of reserpine pretreatment for producing supersensitivity of the nictitating membrane was determined to be 0.1 mg/kg/day i.p. for 14 days. The increase in sensitivity to norepinephrine (0.01 μ g/kg to 100 μ g/kg i.v.) was quantitatively the same after decentralization or after treatment with reserpine. Decentralization and reserpine combined for 14 days produced greater sensitivity than either procedure alone, but less than the great increase in sensitivity caused by denervation. The supersensitivity to acetylcholine (0.01 μ g/kg to 10 μ g/kg i.a.) that resulted from denervation was of more moderate degree, and was quantitatively identical to the supersensitivity to

acetylcholine induced by the combination of decentralization plus reserpine. It is suggested that denervation supersensitivity involves at least two entirely separate mechanisms. One is moderate in degree, nonspecific, and associated with depletion and decentralization. The other involves the failure of the degenerated nerve endings to take up circulating norepinephrine and remove it from the vicinity of the receptors.

West Virginia Medical Center
Morgantown, West Virginia

1882 Welsh, Llewellyn H. & Summa, A. Francis. Determination and identification of p-hydroxyamphetamine as the *O,N*-diacetyl derivative. *Journal of Pharmaceutical Sciences*, 52(7):656-658, 1963.

The determination and identification of p-hydroxyamphetamine in ophthalmic solutions and nasal solutions were accomplished by treating the therapeutic solutions of hydroxyamphetamine acetic anhydride in the presence of sodium bicarbonate and extracting the *O,N*-diacetyl derivative with chloroform. The properties (infrared and ultraviolet spectra and melting point) of the twice recrystallized derivative served to identify the parent substance. An average of 101.2% of the active ingredient was recovered in five assays of a commercial ophthalmic solution.

Food and Drug Administration
U.S. Department of Health, Education,
and Welfare
Washington 25, D.C.

See also: 1685, 1794, 1798, 1823, 1827,
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PSYCHOPHARMACOLOGY ABSTRACTS

Vol. 3 No. 9

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

THE MEMORY OF THE
JULY 1975
DEPARTMENT OF HEALTH

PSYCHOPHARMACOLOGY ABSTRACTS is a publication of the National Clearinghouse for Mental Health Information of the National Institute of Mental Health. It is a specialized information medium designed to assist the Institute in meeting its obligation to foster and support laboratory and clinical research into the nature and causes of mental disorders and methods of treatment and prevention. Specifically, this information service is designed to meet the needs of investigators in the field of psychopharmacology for rapid and comprehensive information about new developments and research results.

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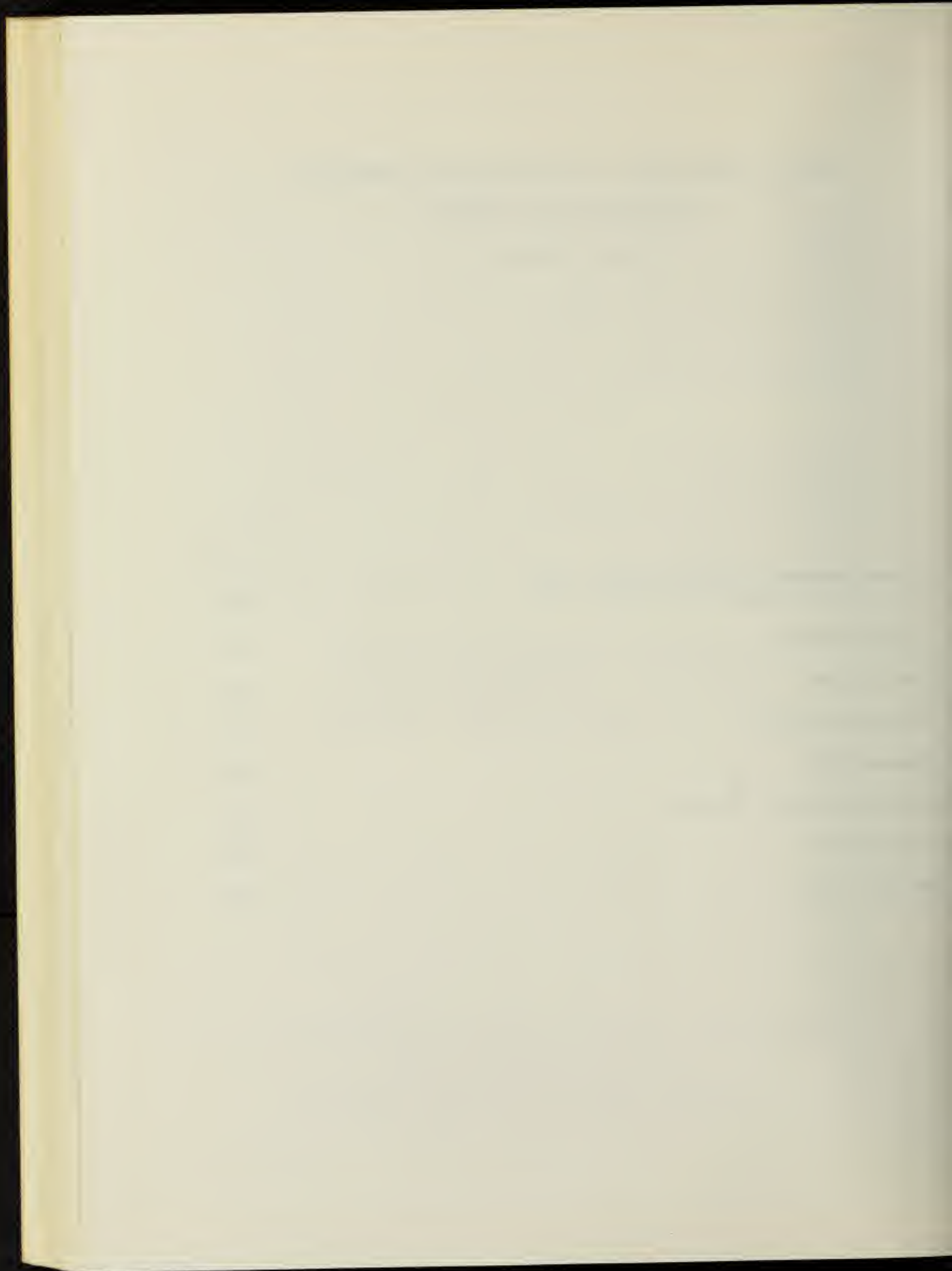
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PSYCHOPHARMACOLOGY ABSTRACTS

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REVIEWS, SUMMARIES, BIBLIOGRAPHIES, GENERAL ARTICLES AND BOOKS

- 1883 Carr, C. Jelleff & Karel, Charlotte. **Metabolic studies and analytical methods for phenothiazine derivatives of psychopharmacologic interest.** Psychopharmacology Service Center Bulletin, 2:71-106, 1963.

Included in this bibliography are summaries of analytical methods for the detection and measurement of the phenothiazine derivatives and their metabolites in animals and man. The cited chemical tests, dealing with the assay or stability of phenothiazine derivatives, may be useful in detecting these drugs and their metabolites in biological fluids or tissues.

National Institute of Mental Health
National Institutes of Health
Bethesda, Maryland

- 1884 Vahia, G. S. **Study of the value of indigenous drugs in psychiatric disorders.** Psychopharmacology Service Center Bulletin, 2:66-67, 1963.

Ayurveda, the ancient system of medicine in India, is discussed in terms of establishing the therapeutic efficacy of the active principles of some of the Ayurvedic drugs in the treatment of psychiatric disorders. Since Ayurvedic prescriptions often consist of drug mixtures, the pharmacologist must study each constituent to find out which is the most active principle. In addition to the usual problems encountered by pharmacologists in the evaluation of drugs, Ayurvedic drugs may produce different therapeutic efficacies due to extraction from the plant at the "improper" time. Sometimes it is also difficult to get the proper drug, since the original Sanskrit name of the drug may be modified differently according to the different languages or parts of the country.

G. S. Medical College
Bombay, India

- 1885 **Chemical synthesis in psychopharmacology.** Psychopharmacology Service Center Bulletin, 2:68-70, 1963.

A list is given of chemicals of psychopharmacologic interest, which have been synthesized or are in the process of being synthesized. In most cases, these are research chemicals that cannot be procured through usual commercial channels. The contractors from whom the chemicals may be purchased are named.

National Institute of Mental Health
National Institutes of Health
Bethesda, Maryland

- 1886 Peck, Harold M. **Preclinical evaluation of drugs for evidence of teratogenic activity.** Journal of Pharmaceutical Sciences, 52(12):1115-1120, 1963.

A review of the method for preclinical evaluation of drugs for evidence of teratogenic activity is presented. Some specific teratogenic agents and their undesirable effects in animals are given. These undesirable effects may be grouped into four general classes: (1) exaggerated primary attributes; (2) secondary attributes; (3) hypersensitivity; and (4) "true" toxicity. The evaluation of new drugs for possible teratogenic properties may be conducted as part of the toxicologic evaluations of the same agents. These studies of new agents should be conducted under reasonable non-toxic daily-dosage schedules in the intact mammal to permit a more valid interpretation of the results.

Merck Institute for Therapeutic Research
West Point, Pennsylvania

- 1887 Rossi, G. Victor. **Synergism with special reference to central nervous system depressants.** Journal of Pharmaceutical Sciences, 52(9):819-832, 1963.

The CNS depressants (analgesics, anesthetics, and hypnotics) are discussed in an attempt to illustrate the general principles and

problems relating to synergism. Narcotic antagonists, synergists, SKF 525-A (β -diethylaminoethylphenylpropylacetate HCl), and the phenothiazines are listed as potentiators of analgesic activity, and the effect of these combinations of drugs on the respiratory and circulatory systems is discussed. Antiemetics, antihistamines, and phenothiazine and nonphenothiazine ataraxics possess a synergistic effect on the anesthetics. Mechanisms of synergic activity, structure-activity relationship of synergists, and biochemical mechanisms of synergists are also included in this review.

Philadelphia College of Pharmacy and Science
Philadelphia, Pennsylvania

1888 Grinspoon, Lester & Greenblatt, Milton. **Pharmacotherapy combined with ether treatment methods.** Comprehensive Psychiatry, 4(4):256-262, 1963.

Combinations of drugs and other modalities of psychiatric treatment have been reported through a brief review of the literature dealing with the use of drugs in relation to electroconvulsant therapy (ECT), occupational therapy, and psychotherapy. The following tentative conclusions were drawn: (1) The combined use of reserpine and ECT may be dangerous. Phenothiazine synergism with ECT remains doubtful. (2) Patients' participation in social interaction and the learning of new skills are possible with combined occupational therapy and drugs. (3) Many patients, due to anxiety reduction by drugs, become complacent and stop working in psychotherapy. Special attention to drug dosage may optimize the usefulness of drugs in this context.

Harvard Medical School
Cambridge, Massachusetts

1889 Kline, Nathan S. **Drugs: A strategic necessity.** Comprehensive Psychiatry, 4(6):387-393, 1963.

An excerpt was cited from President Kennedy's February 5, 1963, message to the Congress, which proposed a new program of Community Mental Health Centers that would make it possible for most of the mentally ill to be successfully and quickly treated and returned to a useful place in society. This program of treatment relies upon the new knowledge and drugs developed in recent years. Most of the mental-hygiene clinics are using verbal psychotherapy alone as the dominant method of treatment.

Many reasons are given for the necessity of drug treatment in community health centers.

Rockland State Hospital
Orangeburg, New York

1890 Elkes, Joel. **The dysleptics: Notes on a no man's land.** Comprehensive Psychiatry, 4(3):195-198, 1963.

A general discussion of the character, use, abuse and dangers of dysleptics is presented. The problem of distribution should be considered by the proper authorities in order to avoid illegal distribution of the compounds. Education of the general public in relation to the potential dangers attending the use of these drugs, and instruction of the physician in the use of antidotes is advised. These drugs may be extremely useful when used in carefully selected patients and under constant and careful medical supervision. Use of dysleptics in an out-patient clinic is contraindicated. These drugs may prove to be a powerful tool in the study of the organization of human behavior and of subjective experience.

National Institute of Mental Health
National Institutes of Health
Bethesda, Maryland

1891 Mandell, Arnold J. **Psychogenic retention of water.** American Heart Journal, 65(4):572-574, 1963.

"Idiopathic pedal edema" in disturbed females has generated interest in the study of psychological factors in the production of water retention states. Brief case histories and experiments are presented in which the psychological state is demonstrated to be a significant variable in water retention and in diuresis.

U.C.L.A. Medical Center
Los Angeles 24, California

1892 Mendlowitz, Milton. **The negative placebo effect in science.** American Heart Journal, 65(6):842-843, 1963.

The negative placebo effect is often not recognized because of the importance given to the skeptic in the current scientific climate. Negative placebo effects may produce inaccurate results if the physician or scientist is prejudiced against the drug.

or the experiment. Emphasis on the positive placebo effect rather than on the negative is urged.

The Mount Sinai Hospital
New York 29, New York

- 1893 Archer, Joel S. & Hicks, Robert G. **Classifications of phenothiazine derivatives.** *British Journal of Anaesthesia*, 35:446, 1963.

A chart showing the relationship of phenothiazine derivatives is presented in order to aid the physician to relate a new phenothiazine to those already being prescribed. The chart is based upon the substitutions occurring at the number 2 position rather than the number 10 position. Three groups depending upon the number 10 side chain are: (1) dimethyl amino propyl side chains; (2) piperazine side chains; and (3) piperidine side chains.

St. Vincent's Hospital
New York, New York

- 1894 Chapman, Loren J. **The problem of selecting drug-free schizophrenics for research.** *Journal of Consulting Psychology*, 27(6):540-542, 1963.

For purposes of research, it is often necessary, but difficult, to obtain a drug-free sample of schizophrenics. In selecting patients to be removed from phenothiazine therapy for purposes of research, 111 male schizophrenics took one of two screening tests (homonym test and breadth of concept test). Of the 52 patients who took one of the two tests successfully, 38 (20 of whom had taken the homonym test and 18 the breadth of concept test) were removed from medication. Their mean age was 39.7 years and mean education was 10.8 years. Chlorpromazine (200 to 800 mg/day) was received by 12 patients, and the other patients were receiving trifluoperazine, prochlorperazine, and thioridazine. During the 6-week drying-out period, 18 patients were returned to medication because of an exacerbation of their psychotic symptoms; these 18 patients were found to have shown greater disorganization of thought than did the remaining 20. These results indicate that a hazard exists for investigators who must rely for their research on patients who do not profit from tranquilizing drugs.

Southern Illinois University
Carbondale, Illinois

- 1895 Fuchs, Margrit. **Persönliche Probleme des Arztes bei der Prüfung neuer Psychopharmaka.** (Personal problems of the physician in testing new psychopharmacological drugs.) *Psychopharmacologia*, 5:77-83, 1963.

The medico-ethical problems of clinical testing of new drugs often lead to an annoying personal conflict in the researcher. The author describes her personal experiences in connection with the testing of a sedative and a neuroplegic. Because precise and systematic observation of psychopharmacological effects requires a great deal of time, a clinical doctor cannot conduct such investigations in conjunction with regular clinical work. The researcher must either share the project with other interested colleagues, or he must renounce routine clinical work and concentrate on the research. In sharing the research, the doctor continues his regular duties and shares responsibility for the research. If the drug proves inapplicable, the clinician's morale is upheld by his regular clinical work. Observations by several different investigators also reduce the influence of personal prejudices. In a solo research project, the factor of the personality of the investigator is not eliminated. However, the researcher has more time to delve into the appurtenant literature. When freed from regular clinical duties, the researcher may encounter envy and jealousy on the part of clinical personnel, whose support he needs for effective conduct of research. The various questions of responsibility of the researcher toward his subject patients are discussed.

Burghölzli Psychiatric University Clinic
Zürich, Switzerland

- 1896 Evans, David A. Price. **Pharmacogenetics.** *American Journal of Medicine*, 34(5):639-662, 1963.

The variability of response by patients to a drug administered in the same way and in the same dosage can be of two different types—continuous or discontinuous variability. The latter gives a bimodal or trimodal curve, which is more suitable for the analysis of genetic factors. Several studies are presented to show how the finding of discontinuous variability in drug action or drug metabolism is related to the genetic systems in man. There appears to be a genetic factor in various racial groups as reported in the cases of actalasia (the actalasia gene is 2.8 times more frequent in Europe than in Japan) or in the polymorphism for isoniazid

REVIEWS 1897-1901

metabolism when the rapid inactivator phenotype was found to be much larger in groups of Japanese subjects than in groups of Caucasian subjects. Hemolytic reactions to drugs are discussed. Glucose-6-phosphate dehydrogenase deficiency and hemoglobin Zurich are inherited characters predisposing to idiosyncratic drug-induced hemolysis. A pharmacogenetic approach can give a clearer understanding of the variety of unusual drug reactions.

University of Liverpool
Liverpool, England

- 1897 Way, E. Leong & Sutherland, V. C.
Pharmacologically active brain substances and their relation to endocrine effects. *Anesthesiology* 24(4):543-562, 1963.

A discussion of recent studies on the physiological significance of pharmacologically active substances in the CNS with emphasis on neuroendocrine and pharmacologic aspects has been presented. Pharmacologically active substances in the brain, such as acetylcholine, norepinephrine, epinephrine, dopamine, 5HT, γ -aminobutyric acid, and substance P, were discussed in terms of the neurogenic release mechanism of the hypothalamic factors. (144 references)

University of California Medical Center
San Francisco, California

- 1898 Geraud, J., Ribaut, L., Rascol, A., & Gayral, L. **Actualités en neuro-psychiatrie.** (*Matters of neuro-psychiatric interest.*) *Toulouse Medical*, 64:221-242, 1963.

The following articles are included in this discussion of matters of neuropsychiatric interest: (1) vascular pathology of the encephalon and the medulla (including surgical possibilities in stenosis of the arterial trunk, vertebro-basilar deficiency, and medullar vascular pathology); (2) paraneoplastic neurological disorders; (3) peripheral neuritis of rheumatoid polyarthritis; (4) spirolactones and cobalt-therapy in serious myasthenia; (5) muscular and electromyographic syndrome; (6) "the dangerous state"; and (7) new psychiatric medicine.

Travail de la Clinique
Neurologique et Psychiatrique
Toulouse, France

- 1899 Frøvig, A. G. **The medical treatment of parkinsonism.** *Acta Neurologica Scandinavica*, 39:169-180, 1963.

A short historical review of the therapy of parkinsonism is presented, followed by an outline of its drug therapy, psychotherapy, physiotherapy, and rehabilitation, which are all fundamental features of medical treatment and should be employed together for best results. The belladonna alkaloids and some synthetic compounds (phenothiazine and benadryl derivatives) are discussed as antitremor drugs.

University of Bergen
Bergen, Norway

- 1900 Pichot, P. **Les médicaments modificateurs du comportement en pratique médicale.** (*Behavior-modifying drugs in medical practice.*) *Presse Medicale*, 71: 811-814, 1963.

In this review of behavior-modifying drugs a list of psychological functions and related pathologic symptoms is followed by a brief discussion of the following groups of drugs: (1) psychotonic; (2) thymoanalept or antidepressant; (3) hypnotics; (4) tranquilizers; (5) neuroleptics; and (6) psychodysleptics. Abnormal personalities, reactions, neuroses, and psychoses are then discussed, and it is concluded that 10 years of psychopharmacology has influenced not only the treatment of mental patients but also the entire field of medicine.

(No address)

- 1901 Gellert, A. **Tranquillizers and the general practitioner.** *East African Medical Journal*, 40(4):134-143, 1963.

In a review of the literature on tranquilizers, information is presented from the point of view of the general practitioner. The tranquilizers were divided into chemical classifications as follows: Rauwolf alkaloids, phenothiazine derivatives, benzhydrol derivatives, hydroxypropanes, chlordiazepoxide, glutarimide derivatives, and others (including chlorprothixene, methylpentynol, and methyprylon). Structural formulas, doses, side effects, and major dangers and indications were given for at least one drug from each group.

Nairobi, Kenya, East Africa

902 Adams, B. G. **Drug profiles. Tran-**
quillizers. Medical World, 99:491-
 95, 1963.

The life histories of several tranquilizing
 drugs, including reserpine, chlorpromazine,
 meprobamate, and chlorthalidone, are
 presented. The life cycles extend
 over a 2- to 6-year period of therapeutic
 investigation. The clinical trial and use
 of the new drug, with its attendant enthu-
 siasm and success, are checked only by
 toxicity. As a result of greater coordina-
 tion and concentration of therapeutic
 investigation, drug values may be defined
 earlier, and epidemics of toxic reaction
 may be curtailed. A change in attitude
 toward psychiatric illness, and the stimu-
 lation of research on the CNS are results
 of the new drug discoveries.

St. Thomas Royal and Maudsley Hospital
 London, England

903 Rogina, V. **Tranquillizers: Success**
and problems. Liječnicki Vjesnik,
 (10):1042-1047, 1963.

A general discussion of tranquilizers,
 including their classification, clinical
 use, and side effects is presented. The use
 of tranquilizing agents has revived the
 interest of the clinician in gaining better
 knowledge of the function and organization
 of the neural systems. Phenothiazine prepa-
 rations that have severe extrapyramidal
 side effects, clinically have a narrower
 spectrum of activity and are less hypnotic
 than those with a wider spectrum of activity.
 It is not clear whether pharmacological
 therapy abolishes only the symptoms or
 whether the course of the basic pathological
 process is also influenced.

Department of Neurology and Psychiatry
 Medical Faculty
 Zagreb, Yugoslavia

904 Jackson, Doniel, Bernard, Lynn A., &
 Bentlif, Philip, eds. **Anti-depres-**
sant drugs. Medical Record and Annals, 56:
 205-218, 1963.

A discussion by two experts of the nature of
 depression and how drugs may help the pa-
 tient and the physician has been presented.
 The case of a 67-year-old woman, who was
 treated for depression with imipramine (25
 mg) and improved markedly, was discussed
 briefly. The principal clinical syndromes

in which depression is a major factor and
 the alerting symptoms of depression were
 listed. The sympathomimetic amines were
 suggested as antidepressants, but they
 possess serious habituating properties. The
 two groups of antidepressants, MAO inhibitors
 and non-MAO inhibitors, were discussed in
 terms of their mechanisms of action, side
 effects, and dosages.

The Methodist Hospital
 Houston, Texas

1905 Kelly, Reginald. **Treatment of dis-**
seminated sclerosis. Physiotherapy,
 49:280-282, 1963.

Curative, preventive, and symptomatic and
 palliative treatments---the three aspects
 of treatment of all conditions---are dis-
 cussed with emphasis on disseminated scler-
 osis. To these three aspects, a fourth,
 more important than any of the others in
 the condition of disseminated sclerosis,
 has been added. This new aspect concerns
 the management of the patient as an indi-
 vidual faced with a frustrating, frighten-
 ing disease. The physiotherapist must ap-
 proach this type of patient with confidence
 that they will recover.

National Hospitals for Nervous Diseases
 Maida Vale, London, England

1906 Unger, Sanford M. **Mescaline, LSD,**
psilocybin, and personality change,
a review. Psychiatry, 26(2):111-125, 1963.

A review is presented of the literature on
 psychedelic drug experiences. The subjec-
 tive effects of mescaline, LSD-25, and
 psilocybin are similar, equivalent, or
 indistinguishable. The invariant drug reac-
 tions in this paranormal experience are
 alterations in visual experience and in
 experience of self. It has become clear
 from the systematic variability reported in
 subject and patient reactions---in both
 affective and ideational dimensions of drug
 experience---that factors other than "per-
 sonality" are also at issue. The environ-
 mental setting, the attitude of the thera-
 pist, and the attitude and expectations of
 the subject account for variable responses.
 Rapid personality changes, both with and
 without drugs, are discussed. The use of
 LSD in the treatment of alcoholics and sex
 perverts, as a utilization of a new concept
 in psychotherapy, is discussed.

National Institute of Mental Health
 National Institutes of Health
 Bethesda, Maryland

REVIEWS 1907-1910

- 1907 Savage, Charles, Stolaroff, Myron, Harman, Willis, & Fadiman, James. **Caveat! The psychedelic experience.** Journal of Neuropsychiatry, 5(1):4-5, 1963.

Precautions in the use of LSD-25 are briefly discussed. These precautions include the following: (1) The therapist should gain the trust of the patient before administering the drug. (2) The LSD treatment program should include adequate followup and support. (3) All personnel who work with the patients, including the therapist, should have had personal experience with LSD. (4) The therapists should observe other LSD sessions. (5) Latent and overt schizophrenic patients and patients with cyclic disturbances should not be treated with LSD as outpatients. (6) Borderline patients, paranoid, and depressed patients often require conventional psychotherapy before and after a psychedelic experience.

International Foundation for Advanced Study
Stanford University
Stanford, California

- 1908 **Dispute over hallucinogenic compounds reaches climax.** Journal of the Mississippi State Medical Association, 4:320-321, 1963.

The misuse of consciousness-expanding drugs resulted in the dismissal of two professors at Harvard University. Since the Government does not license research with psychedelics, except that sponsored by the Government, an active research and training program is being continued in Mexico. A suggestion is made that LSD-25 be restricted to investigators in institutions and hospitals.

(No address)

- 1909 Launay, J. **Actual research at the psychopharmacology center of Charenton-Saint Maurice (Paris).** Psychiatric Quarterly, 37(4):618-630, 1963.

The Center of Experimental Psychology of the Sorbonne in Paris has for the last 10 years devoted its activities to two main fields: (1) the study of new therapeutic drugs offered to psychiatry; and (2) the study of biological and biochemical factors involved in the genesis of psychosis, which includes animal experimentation with indole derivatives and serotonin, studies on identification of catatonogenic substances in human

bile, and the immuno-allergenic study of pulmonary tuberculosis in psychiatric establishments. These activities are discussed in terms of research in animals and clinical experimentation.

Sorbonne
Paris, France

- 1910 Rickels, Karl. **Pharmacotherapy of depression. (A questionnaire survey of a group of psychiatrists and general practitioners).** Psychosomatics, 3(5):1-7, 1963.

In an attempt to randomize out many variables which appear in controlled studies, a questionnaire was sent to 300 psychiatrists and 100 general practitioners to collect a large sampling of data with relation to the use of antidepressants in depression. This survey included the following drugs: dextroamphetamine, Deprol (400 mg meprobamate and 1 mg benactyzine), meprobamate, imipramine drug combinations, and five MAO inhibitors (iproniazid, isocarboxazid, nialamide, phenelzine, and phenylisopropyl hydrazine). The following information was obtained: overall impression of the drug efficacy, estimated number of patients treated, ratio of patient improvement, number of inpatients and outpatients, drug effects on anxiety, and ratings of side reactions. Of the 128 questionnaires returned by psychiatrists, only 89 used drugs in the treatment of depression and of the 27 general practitioners who returned the questionnaires, 2 used drugs for treatment of depression. Both groups of physicians reported dextroamphetamine as the least effective agent and meprobamate, and particularly Deprol as being most effective in the symptomatic and adjunctive treatment of the mild to moderate depressions. Imipramine is primarily effective in treating the more severe, or somewhat retarded, depressions. Imipramine in lower doses was effective in reducing anxiety in the mildly neurotic depressed patients. The least amount of side reactions were reported for meprobamate and Deprol. Side reactions were more marked with imipramine, dextroamphetamine, and the MAO inhibitors. These data compare quite favorably with data found in controlled double-blind studies.

University of Pennsylvania
Philadelphia, Pennsylvania

CLINICAL STUDIES

1911 Bishop, M. P., Gallant, D. M., & Steele, C. A. A controlled evaluation of benzquinamide: Behavioral toxicity with high dosage levels in schizophrenics. *Current Therapeutic Research*, 5(5):238-244, 1963.

A double-blind procedure was used to test the relative efficacy of the experimental compound, benzquinamide, as compared with chlorpromazine and placebo in the treatment of hospitalized, chronic schizophrenic patients. Thirty patients, 16 males and 14 females, ranging in age from 29 to 45 years, were selected from a population of 144 chronic schizophrenic patients who had received thorough psychiatric, psychological, neurological, medical, and laboratory examinations. The 30 patients selected had been off all medication for at least 60 days before being assigned 10 to each of the three medications. Patients received from 200 to 1,200 mg benzquinamide daily and from 200 to 500 mg chlorpromazine daily. Drugs and placebo were supplied in capsules of identical appearance. The Lorr Psychiatric Rating Scale, Overall and Gorham Brief Psychiatric Rating Scale, subjective ratings of improvement by evaluating psychiatrists, and the Tulane Test Battery were used to evaluate results. Biochemical and laboratory data included complete blood count, hematocrit, sedimentation rate, fasting blood sugar, urinalysis, and liver function test. Perhaps the most significant finding of this study was the appearance of severe behavioral toxicity in 3 of the 10 patients receiving benzquinamide. The loss of four patients from the benzquinamide group precluded reliable statistical analysis. Chlorpromazine produced some degree of improvement in 8 of 10 patients, whereas only 1 patient in the benzquinamide group was rated as improved. Two patients on benzquinamide developed weakness and profuse perspiration as side effects at the 1,200-mg daily dose. In view of this finding, it is recommended that benzquinamide dosages should not exceed 800 mg daily.

Tulane University
School of Medicine
New Orleans, Louisiana

1912 Overall, J. E., Hollister, L. E., Bennett, J. L., Shelton, J., & Caffey, E. M., Jr. Benzquinamide in newly admitted schizophrenics: A search for patients best treated with a specific drug. *Current Therapeutic Research*, 5(7):335-342, 1963.

Fifty-four male, newly admitted schizophrenics with no complicating medical illnesses or brain damage were treated with benzquinamide, 200 to 1,400 mg daily, in capsule or ampule form. Ten patients were withdrawn from the 6-weeks study before 4 weeks of treatment and were, therefore, not included in the analysis of drug effects. Evaluation of patient change was accomplished by two measurements—the Brief Psychiatric Rating Scale (BPRS) and a Nurse's Evaluation Form (twice weekly). Conventional hypnotics were allowed, as needed, and anticholinergics or antihistamines were allowed for treating extrapyramidal reactions. Prior to treatment, patients had a urinalysis, complete blood count, and a battery of hepatic tests, and during each week of treatment, a total or differential leucocyte count and a serum glutamic oxalacetic transaminase titer were obtained. Patients showed significant improvement in 11 of 16 symptom areas measured by the BPRS, those showing most change being emotional withdrawal, conceptual disorganization, tension, suspiciousness, hallucinatory behavior, unusual thought content, and blunted affect. Nurses' evaluations also showed a similar trend toward improvement. Side effects encountered with benzquinamide included weakness and fatigue (14 of 44 patients), anxiety (13), drowsiness (12), agitation (9), and extrapyramidal syndromes (9).

Manhattan, Kansas

1913 Matthey, William E. Combination therapy for relief of anxiety and depression. *Current Therapeutic Research*, 5(6):310-318, 1963.

A clinical trial was conducted on 117 patients, 43 males and 74 females, ranging in age from 10 to 74 years, and suffering

CLINICAL STUDIES 1914-1915

from anxiety and depression, in order to ascertain which of four experimental combined dosages of perphenazine and amitriptyline has the best therapeutic value. The four experimental combinations and the number of patients receiving each were: (1) 2 mg perphenazine and 10 mg amitriptyline, 5 patients; (2) 4 mg perphenazine and 10 mg amitriptyline, 11 patients; (3) 2 mg perphenazine and 25 mg amitriptyline, 86 patients; and (4) 4 mg perphenazine and 25 mg amitriptyline, 15 patients. The usual dosage was three tablets daily, so that the patients received 6 or 12 mg perphenazine and 30 or 75 mg amitriptyline daily. The duration of therapy ranged between 1 week and 14 weeks, with a mean of 9 weeks. The No. 1 combination proved to be below the therapeutic level, with four of five patients failing to respond to therapy. The No. 2 combination was fairly effective in some patients, but the amount of amitriptyline was generally inadequate for those whose major problem was depression. The most favorable combination was No. 3, with anxiety and depression diminishing in all but three patients during therapy. The No. 4 combination produced generally good results, although the incidence of side effects was higher than in any of the other three groups. There were no side effects with the first combination; 10% of the patients reported side effects with the second combination, 21% with the third combination, and 40% with the fourth combination. The side effects included diarrhea, dizziness, insomnia, drowsiness, and pruritus. These side effects disappeared after 1 or 2 days, without reduction of dosage, in 18 of the 25 patients; 6 of the others were able to continue treatment at reduced dosage.

St. Vincent's Hospital
Montclair, New Jersey

1914 Downing, Robert W., Ebert, John N., & Shubrooks, Samuel J. Effect of phenothiazines on the thinking of acute schizophrenics. *Perceptual and Motor Skills*, 17(2):511-520, 1963.

This study investigates the effect of chlorpromazine, thioridazine, fluphenazine, and placebo upon the appropriateness of thinking in a group of 37 acute schizophrenics. There were 12 white males, 7 white females, 8 Negro males, and 10 Negro females, ranging in age from 17 to 44 years, who took part in the study. Patients were randomly assigned to the placebo or to one of the three drugs, and a double-blind procedure was followed. Dosage level varied

from a minimum of 200 mg to a maximum of 1,600 mg per day for chlorpromazine and thioridazine, and from 2 mg to 16 mg per day for fluphenazine. A test was given that measured the extent to which associatively linked distractors intruded themselves inappropriately into the generation of concepts, both upon admission to the hospital and after 6 weeks of treatment. Fluphenazine and thioridazine produced a decrement in distractor-produced errors greater than that resulting from placebo. Changes produced by chlorpromazine did not differ significantly from those of the placebo. Some factors that may possibly account for the effectiveness of fluphenazine are discussed, but such explanations could not be reconciled with the effectiveness of thioridazine.

University of Pennsylvania
Philadelphia, Pennsylvania

1915 Court, J. H. & Cameron, I. A. Psychomotor assessment of the effect of haloperidol. *Perceptual and Motor Skills*, 17:168-170, 1963.

Clinical and psychological findings are reported for successful administrations of haloperidol in 10 cases of manic depression and schizophrenic excitement. Haloperidol was given parenterally initially for 3 to 26 days, all patients receiving between 7.5 to 25 mg; oral administration followed, and in eight cases, a maintenance dose (1.5 to 5 mg daily) was continued at discharge. Four psychomotor tests were administered on three occasions during treatment in an attempt to distinguish therapeutic response from side effects. Psychomotor tests' results from the 10 subjects studied showed good internal consistency and compare closely with results in larger groups. All patients improved, but all developed marked side effects. Parkinsonism was the first observable change; akinesia was the dominant syndrome. In some cases this was severe, reducing the patient to a state of incapacity, characterized by mask-like faces, loss of arm swing, shuffling feet, shortened and slow pace, and flexed spine.

Crichton Royal
Dumfries, England

- 1916 Blake, Alton D., Jr. **Treatment of gastrointestinal disorders with a combination of trifluoperazine and isopropamide.** *Clinical Medicine*, 70:1461-1465, 1963.

Trifluoperazine and isopropamide were used in the treatment of 118 patients (40 males and 78 females, ranging in age from 20 to 70 years) with gastrointestinal distress caused or aggravated by anxiety and tension. In the 56 patients whose illness was acute, there were prominent signs of emotional distress—nervousness, anxiety, mild agitation, or frustration. In the 62 patients whose illness had been present for 5 years or more, emotional symptoms were more subdued, often with an overlay of depression or an air of hopelessness. The patients were started on tablets, each tablet containing a ratio of 1 mg of trifluoperazine to 5 mg of isopropamide, given b.i.d. If more complete control of emotional factors became necessary, the ratio of trifluoperazine was increased to 2 mg. Treatment ranged from 2 weeks to 60 weeks; most patients were treated 10 months or longer. Except for 22 peptic ulcer patients who needed antacids, diet was the only other therapy used. Results were considered good in 78%, fair in 7%, and poor in 5%. The drug combination appeared to be particularly effective in 62 patients with a chronic condition that had failed to respond to previous treatment. No particular side effects were observed except for dry mouth, which occurred in 22 patients.

Ryan Mawr, Pennsylvania

- 1917 Goodley, Eugene L. **Clinical evaluation of combined orphenadrine-fluphenazine in acute and chronic musculoskeletal disorders.** *Clinical Medicine*, 70:1843-1846, 1963.

A therapeutic comparison of the oral efficacy of a skeletal muscle spasmolytic, orphenadrine-fluphenazine, and a muscle relaxant drug, methocarbamol, was undertaken in 25 patients with acute and chronic musculoskeletal disorders. The patients (4 men and 21 women, with ages ranging from 21 to over 70 years) were given orphenadrine-fluphenazine (1 tablet b.i.d.) or methocarbamol (three to four 5-g tablets q.i.d.) for alternate 1-week periods. Fair or good responses to orphenadrine-fluphenazine were noted in 65% of the total group. Of the 12 patients not benefited, 11 had osteoarthritis or chronic lumbar strain. Methocarbamol was effective in only 30% of the total group. Of the 25 patients not responsive to methocarbamol, 16 had osteoarthritis or chronic

low back strain. Drowsiness and dizziness were noted in six patients on the orphenadrine-fluphenazine treatment and in seven patients during therapy with methocarbamol. On the basis of these observations, it appears that orphenadrine-fluphenazine is a therapeutically advantageous muscle relaxant.

Los Angeles, California

- 1918 Blackman, Benjamin. **The adjunctive role of diazepam in the treatment of depression.** *Clinical Medicine*, 70:1495-1500, 1963.

A trial was undertaken to ascertain the value of diazepam therapy as an adjunct to psychotherapy in treating depressed patients. Diazepam was administered (5 mg t.i.d. for a period of 4 to 6 weeks) to 68 patients (19 males and 49 females), ranging in age from 17 to 75 years, who were currently receiving psychotherapy in private-office practices. Specifically selected for the study were 47 patients with depressive reactions, whereas the inclusion of patients with schizophrenic, manic, and acute anxiety reactions and personality disorders was designed intentionally to study the comparative response of the drug in other emotional illnesses. Of the 47 patients suffering from depressive reactions, many had experienced recurrent episodes of depression ranging from many weeks to months, and they had received previously ECT treatment in one or more series over a period of years. Fifty-seven percent of the 47 depressed patients made good to excellent response, whereas 33% of the 20 other patients responded satisfactorily to the drug. Side effects of the treatment were few. Ten patients complained of tiredness, three of sleepiness, and two of both tiredness and sleepiness. One patient complained of dizziness, and one developed an erythematous eruption, which may have been caused by another drug that he was taking concurrently. These undesirable effects disappeared in a day or two after drug discontinuation.

Chicago, Illinois

- 1919 Lamphier, Timothy A. **The evaluation of nialamide in postoperative depressive states.** *Clinical Medicine*, 70:1467-1472, 1963.

The general pharmacology and its effectiveness in the treatment of preoperative and postoperative depressive states have been

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discussed. Nialamide (50 to 75 mg/day) was given to 91% of 102 patients with postoperative depression, and the other 9% received (100 to 200 mg/day). Most of the patients were 40 to 59 years of age, and 60% were women. The period of treatment ranged from 4 to 15 days, and results were good to excellent in 85%, fair in 12%, and poor in 3%. Side effects (nausea or rash), which occurred in the 3% group, were quickly relieved by drug withdrawal. It was concluded that nialamide is an excellent therapeutic postoperative agent for the relief of depressive states and is of great value in producing cooperative patients during the postoperative period.

Boston, Massachusetts

1920 Sprechel, Daniel. A quantitative comparison of electroconvulsive therapy with hexafluorodiethyl ether. *Journal of Neuropsychiatry*, 5(2):32-37, 1963.

Twenty-four severely depressed patients, 11 males and 13 females, were selected from a population of 80 hospitalized white patients needing convulsive therapy, for a quantitative comparison of ECT and Indoklon therapy. The conventional diagnostic entities were: psychotic reaction, depressed type (16 patients); psychotic depressive reaction (5 patients); and manic depressive reaction, depressive type (3 patients). Both groups of patients were prepared identically for treatment and both received atropine 1.2 mg 30 to 45 minutes prior to treatment. In the ECT group, succinylcholine 20 to 30 mg was given i.v., and when signs of relaxation occurred, ECT was administered, followed immediately by use of a hand-bellows respirator until the patient resumed normal breathing. In the Indoklon group, the succinylcholine was followed immediately by 4 to 8 cc of 5% Indoklon in the first four patients and 2 to 4 cc of 10% Indoklon in the remainder of this group. When myoclonic jerking appeared, the injection was stopped, and the amount of drug administered was recorded. A grand mal seizure was produced in every case. The grading scale for depressive reaction, the MMPI D Scale, the Cutler and Kurland Scale, and the Wechsler Memory Scale were used to evaluate the results of the two treatments. Clinically, there was no detectable difference in the results with the two treatments. All patients improved satisfactorily, and all were discharged from the hospital. In the 3-month followup, 11 patients in the

Indoklon group and 8 patients in the ECT group were apparently healthy and functioning in their premorbid capacity.

Tulane University School of Medicine
New Orleans, Louisiana

1921 Maddox, Paul F. Treatment of emotional disorders with chlorprothixene. *Journal of Neuropsychiatry*, 5(1):92-95, 1963.

In the present trial, chlorprothixene was administered to 67 patients seen in private psychiatric practice for various emotional disorders, which included anxiety, depression, and psychoneurosis. Chlorprothixene, in conjunction with psychotherapy, was administered orally in 10- to 50-mg doses, with total daily doses ranging from 25 to 100 mg. Twenty-two patients received a single daily dose of 50 mg at bedtime, whereas most of the others received multiple doses of 10, 25, or 50 mg. The average duration of treatment was approximately 40 days. Fifty-three, or 79.1%, of the patients responded favorably to chlorprothixene treatment, with marked clearing of symptoms occurring in most cases. Ten (14.9%) of the total had a fair response, and four (6.0%) had no improvement with chlorprothixene. Only one side effect was observed throughout the study—a patient with anxiety expressed drowsiness, which disappeared upon reduction of dosage. Two case histories, a 60-year-old female diabetic with acute anxiety and a 71-year-old female with senile psychosis, are cited as specific case samples of chlorprothixene treatment.

Campton, Kentucky

1922 Ban, T. A. & Schwarz, L. Systematic studies with levomepromazine. *Journal of Neuropsychiatry*, 5(2):112-117, 1963.

The pharmacological, pathophysiological and psychophysiological findings of levomepromazine were reviewed, and a case study of patients with depressive syndromes who were treated with levomepromazine was reported. The patients (15 males, 5 females) began with 15 mg/day p.o., which was increased to 30 mg/day and then to higher doses ranging from 75 to 150 mg. The treatment continued for 10 weeks. In 80% of the patients, improvement was observed within 2 weeks after commencement of treatment. The greatest improvement occurred between the fourth or eighth week of therapy. The patients with

schizoaffective disorders (six patients) and involuntional melancholia (five patients) showed the best results. Of the four patients in the manic-depressive group, three showed improvement, and two of the five patients with neurotic-depressive reactions responded favorably to treatment. The most frequent side effects encountered were extrapyramidal symptoms (akathisia and dyskinesia). A skin reaction also occurred in one case, which responded to antiallergic (diphenhydramine) therapy within 24 hours.

Meridun Protestant Hospital
Quebec, Canada

1923 Nussbaum, Kurt & Kurland, Albert A. Bis (2,2,2-trifluorethyl) ether (Indoklon) modified with succinylcholine (Anectine) as a convulsant in psychiatric treatment. *Journal of Neuropsychiatry*, 5(2):143-149, 1963.

A psychiatric patient was given succinylcholine (SCC) as a seizure modifier in intravenous Indoklon, and the results have been reported. The 25-year-old male (weight, 159 pounds) was diagnosed as a chronic, undifferentiated schizophrenic with borderline intelligence and with a possibility of petit mal epilepsy. After treatment with chlorpromazine and benzopropine methanesulfonate, the patient remained depressed and preoccupied; he was, therefore, placed on the SCC-Indoklon treatment. Atropine or scopolamine hydrobromide was given as preliminary medication. The patient received SCC followed by Indoklon solution on 8 days within a 3-week period. The dosage of Indoklon solution, 1 cc on the first day, was reduced to 7 cc on the second day, 6 cc on the third and fourth days, 5 cc on the fourth (repeat treatment), sixth, and seventh days, with doses of 6 cc on the intermittent days. The SCC (20, 30, or 40 mg) was given in a separate syringe on all treatment days. The patient became more cheerful with each treatment, but some impairment of memory was observed. For best therapeutic results and retention of memory, grand mal seizures could always be obtained in convulsive therapy. It was discovered that by increasing the respiratory paralysis with a larger dose of SCC (40 mg), smaller amounts of Indoklon were sufficient to produce convulsions. Before treatment the patient's EEG showed only meager abnormalities; 3 weeks after treatment the EEG tracing showed an normal amount of background theta range activity with no localization or lateralization. Although valuable clues were gained

for the prevention of prolonged seizures, the most effective dosage and ratio of the two drugs was not determined.

Spring Grove State Hospital
Baltimore 28, Maryland

1924 Solomon, Samuel. Clinical trial of an antipsychotic agent with a low toxic index: Carphenazine. *Journal of Neuropsychiatry*, 5(1):80-85, 1963.

A clinical assessment of carphenazine was made using 457 Negro mental patients, of whom 356 were schizophrenic and 101 had other mental disorders. There were 331 women and 126 men, most patients being between 20 and 50 years of age. All other medications were withdrawn prior to the administration of carphenazine. Blood tests and liver function studies were made. The dosage ranged from 25 mg to 200 mg daily, with the optimum dosage being between 100 and 200 mg daily. Evaluations were made in terms of marked, moderate or slight, and no improvement. Ninety-one percent of the schizophrenic patients were either markedly or moderately improved, with paranoid, catatonic, and undifferentiated types showing the most response, and with hebephrenia showing the least response. Discharge rate for schizophrenia was 20%, and there was a sustained remission from 6 months to a year. Seventy-four percent of the other mental disorders were either markedly or moderately improved, with manic-depressive psychosis as the most responsive, followed by the brain syndromes. There was a positive cumulative effect of the drug, and the maximum therapeutic effect was attained at 200 mg daily. Side effects were minimal, with extrapyramidal symptoms, drowsiness, hypotension, and transient facial edema being reported. No blood dyscrasias or liver abnormalities occurred.

Western State Hospital
Bolivar, Tennessee

1925 Kiloh, L. G., Roy, J. R., & Carney, M. W. P. A pilot trial of G. 33040 in the treatment of depressive illness. *Journal of Neuropsychiatry*, 5(1):18-20, 1963.

A preliminary assessment of G. 33040, a dibenzazepine compound that is chemically similar to imipramine, was made in a study using 28 patients with endogenous depression (13 females and 15 males, with a mean age of 53.5 and 55 years, respectively) and 34 patients suffering from neurotic depression (11 males and 23 females, with a mean

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age of 48 and 43 years, respectively). The dosage varied from 75 to 200 mg daily. Initial assessment was made after 3 weeks, and all cases were followed for at least 3 months. Cases classified as symptom-free or as showing marked improvement were grouped as showing a good response; the remaining cases were grouped as showing a poor response. Sixteen of the 28 cases of endogenous depression showed a marked improvement, and 12 remained well for 3 months, whereas only 8 of the 34 cases of neurotic depression showed a good initial response and 4 relapsed by the end of 3 months. It appeared that larger doses of G. 33040 were associated with a quicker and more profound response. The side effects were mild, with dizziness, sleepiness, or fatigue being the most prominent. The G. 33040 is more effective in the treatment of endogenous depression than of neurotic depression.

Prince Henry Hospital
Little Bay, Sydney, Australia

1926 Bishop, M. P., Buddington, R. W., Robinson, W. G., & Silva, F. A comparison of SKF-7261 and trifluoperazine (stelazine) in the treatment of chronic schizophrenic patients. *Journal of Neuro-psychiatry*, 5(1):28-32, 1963.

The therapeutic effects of an experimental phenothiazine compound, SKF-7261, and trifluoperazine were compared in a double-blind study using 38 chronic, schizophrenic patients (20 males and 18 females) divided into two groups of 19 each. The ages ranged from 22 to 49 years. All subjects received a placebo the first week, followed by either SKF-7261 (3 to 6 mg/day) or trifluoperazine (15 to 24 mg/day) for an 8-week period. The Lorr psychiatric rating scale was used for psychiatric evaluation, and a significant degree of improvement was noted when both drugs were used, with no differences between the drugs. The improvement was noted in conceptual disorganization, perceptual distortion, and motor disturbances. Psychological performance involving a battery of five tests, including perceptual speed, immediate memory, comprehension, psychomotor speed, and general test behavior, revealed a significant improvement in psychological functioning with both SKF-7261 and trifluoperazine. There was no difference in performance between the two drugs. Routine laboratory evaluations (blood, urine, and liver function studies) showed no significant change. Side effects noted in 10 patients on trifluoperazine were akathisia, restlessness, resting tremor, occasional dystonic

symptoms, and rarely transient hypotension. Side effects noted in SKF-7261 were less severe. All side effects were controlled by benztropine methane sulfonate. The clinical effects of these drugs appear similar.

Tulane University School of Medicine
New Orleans, Louisiana

1927 Weintraub, Walter & Aronson, Harriet. Clinical judgment in psychopharmacological research. *Journal of Neuropsychiatry*, 5(1):65-70, 1963.

A double-blind study comparing the antidepressant effects of imipramine (150 mg t.i.d.) and placebo containing 0.1 atropine (given in the same number of tablets as imipramine) was carried out on 72 depressed patients (19 to 73 years of age, mean age 50.6). Thirty-four were assigned to the placebo group (11 males and 23 females) and 38 to the drug group (18 males and 20 females). Judgments on the degree of initial depression, diagnosis, and degree of improvement were made by the chief resident and the resident physician of a psychiatric institute. Psychological tests, including the MMPI, were administered to all patients before and after the 4-week experimental period. There was poor agreement among the judges (therapist and chief resident) as to the level of depression on admission. After 4 weeks of treatment, ratings were made by the therapist and chief resident according to remission or greatly improved, moderately improved, and no improvement or worse. The therapists rated the imipramine group as significantly better than the placebo group whereas the chief residents' ratings showed very little difference between the two. The MMPI showed a significant difference in degree of improvement in favor of imipramine. Side effects of imipramine were mild, and only one patient was dropped because of severe hypotension. Psychiatric judgment was influenced by length of experience, psychiatric orientation, intensity of involvement with the patient, and lack of interest in psychopharmacology.

University of Maryland Psychiatric Institute
Baltimore, Maryland

- 1928 Rondepierre, J. J., Bornstein, S., & Jolivet, B. *La trifluopérazine a doses faibles. Son emploi en service psychiatrique ouvert.* (Trifluoperazine in low doses. Its use in an open psychiatric ward.) *Annales Médico-Psychologiques*, 120(1):96-100, 1963.

The therapeutic effects of trifluoperazine were observed in 44 patients (16 alcoholic and 28 nonalcoholic) with anxiety. Dosage was between 3 and 6 mg, and treatment lasted from 15 days to 2 months. In certain cases, administration of a light hypnotic or classic treatment of alcoholism accompanied trifluoperazine therapy. Of the 44 patients, excellent or satisfactory improvement was observed in 31 cases, whereas 13 showed no change or slight improvement. The drug seemed to act mainly on anxious tension, and favorable results were similar in both the alcoholic and nonalcoholic groups. No side effects were noted.

(No address)

- 1929 Gayral, M. L., Stern, H., Bardis, Cl., & Robert, P. *Traitement des états de depression mentale par l'amitriptyline (laroxyl).* (Treatment of depressed mental states with amitriptyline.) *Annales Médico-Psychologiques*, 121:447-452, 1963.

In a discussion of various clinical trials of the use of amitriptyline in depression, the dosage, tolerance, and associated treatments are emphasized. Amitriptyline is given at a dose of 75 to 200 mg daily p.o. in milder forms of depression and i.m. in the beginning of treatment of more severe forms. Tolerance to the drug is good, and side effects were mild, and included infrequent dizziness, somnolence, dry mouth, asthenia, and hypotension. Treatment with amitriptyline has been successfully combined with treatment by levomepromazine, ECT, chlordiazepoxide, fluphenazine, isocarboxazid, tranlycypromine, and other drugs. It was found that amitriptyline is an important antidepressant.

(No address)

- 1930 Kammerer, Th., Singer, L., & Poirot, J. P. *L'amitriptyline dans les états dépressifs.* (Amitriptyline in depression.) *Annales Médico-Psychologiques*, 121:440-447, 1963.

To observe the effect of amitriptyline on depressed patients, 36 inpatients between 23 and 70 years old; 35 females and 1 male)

who showed different forms of depression were examined daily while receiving the drug. Amitriptyline was administered p.o. in a dosage of about 150 mg/day. Results were as follows: cures (15 cases): noticeable improvement (8 cases); slight improvement (1 case); no improvement (8 cases); and aggravation of condition (4 cases). Eighteen patients continued treatment with amitriptyline at home, whereas 14 substituted a commercial antidepressant and 4 discontinued treatment while still in the hospital. Side effects, although minimal, included trembling of extremities, asthenia, and somnolence. It was concluded that amitriptyline is a useful drug in the treatment of depression, and that it possesses light sedative and anxiolytic effects that should not be overlooked.

Clinique Psychiatrique du Centre Hospitalo-Universitaire de Strasbourg
Strasbourg, France

- 1931 Margat, P. & Creton, M. *Le chlordiazépoxyde et le traitement de l'alcoolisme.* (Chloridazepoxide and the treatment of alcoholism.) *Annales Médico-Psychologiques*, 12(1):92-96, 1963.

To determine the use of chlordiazepoxide in the treatment of alcoholism, the drug was administered to 40 patients with delirium, pre-delirium, or simple alcoholism. Chlordiazepoxide was administered by parenteral route for about 2 to 4 days, and the results were as follows: 26 excellent; 9 good; 1 mediocre; and 4 none. No side effects were reported, and it was concluded that chlordiazepoxide, accompanied by the classic treatment of alcoholism, is excellent in calming agitation, reducing anxiety, and in preventing the reappearance of disorders. Individual cases are briefly described.

(No address)

- 1932 Chatagnon, C. & Chatagnon, P. A. *Au sujet de l'ammoniémie au cours d'états psychotiques et névrotiques.* (Ammoniaemia in psychotic and neurotic states.) *Annales Médico-Psychologiques*, 121:468-473, 1963.

Ammoniac level, N-glutamine level, and pH were measured in venous blood of 34 women (35 to 83 years old) with psychosis or neurosis. An accompanying table shows name, age, diagnosis, and pertinent data about each patient. In an effort to correlate

CLINICAL STUDIES 1933-1936

ammoniemia with psychotic and neurotic conditions, it is suggested that the origin of an increase of ammoniac in the blood in hepatic patients is probably related to the deterioration of ablation mechanisms. It was found that ammoniemia is present most often in the precoma or coma stages of severe hepatic diseases, or in the psychotic and neurotic states that are accompanied by liver disorders.

Laboratoire Central de Biologie et de Biologie Nerveuse de l'Hôpital de Maison Blanche
Neuilly-sur-Marne, France

- 1933 Bardis, Cl., Gayral, L., Stern, H., & Robert, M. P. **Indications thérapeutiques de la fluphénazine. (Therapeutic information about fluphenazine.)** Annales Médico-Psychologiques, 121:458-462, 1963.

Typical cases of delirious melancholy, long-term delirium, and paranoid schizophrenia are briefly described to show some therapeutic effects of fluphenazine. Results of observations of 27 cases of various psychotic and neurotic conditions are reported. It was found that fluphenazine acts, essentially, in the reduction of psychotic elements, pathologic symptoms, morbid reactions, and delirious behavior, but it has little or no effect on other symptoms. It was found to be ineffective in the treatment of depression and anxiety, and may possibly induce anxiety in certain patients.

(No address)

- 1934 Roux, G., Mouton, P., Bardis, Cl., & Gayral, L. **Emploi de l'haloanisone chez les enfants arriérés non épileptiques. (Use of haloanisone in retarded non-epileptic children.)** Annales Médico-Psychologiques, 121(1):84-91, 1963.

The effects of haloanisone in 30 retarded, nonepileptic children are reported. Treatment lasted from 3 weeks to 4 months, and drug dosage was between 5 mg to 30 mg daily. Sedative action was observed about 24 to 72 hours after administration, and symptoms recurred rapidly after the treatment was discontinued. Haloanisone was most effective in children whose disorders comprised a large psychic element (i.e., attitudes and reactions), whereas problems based

exclusively on motor disorders were not influenced by the drug. The only important side effect noted was somnolence. Individual cases are discussed briefly.

(No address)

- 1935 Borel, J., Lauzel, J. P., Hanus, M., & Israël, P. **A propos d'une démente paranoïde guérie par une cure neuroleptique de quinze mois (Fifteen-month neuroleptic cure of paranoid dementia.)** Annales Médico-Psychologiques, 2:57-59, 1963.

A case history is presented of a 30-year-old man with paranoid dementia who was cured with neuroleptic medication in 15 months. He was first given chlorpromazine (100, 450, and 600 mg daily) and showed some, but not full, recovery. He was later given thioproperazine (10 to 60 mg), but could not tolerate the drug despite simultaneous administration of ethopropazine. Treatment was reduced to only 30 mg thioproperazine with 200 mg chlorpromazine. Hypertonia, impatience, akinesia, and anxiety caused discontinuation of the treatment for 2 months, which was followed by treatment with only thioproperazine and ethopropazine. Treatment was again discontinued, then reestablished at the same dosage (30 mg thioproperazine). The patient's long-term use of thioproperazine has been closely checked, and he is completely cured. The importance of looking for a complete rather than for a partial cure for paranoid dementia is emphasized.

(No address)

- 1936 Delay, Jean, Deniker, P., Leyrie, J., & Conté, C. **Intérêt de l'utilisation de la fluphénazine dans le traitement des états schizophréniques. (Use of fluphenazine in the treatment of schizophrenia.)** Annales Médico-Psychologiques, 121:452-457, 1963.

Results are presented of a clinical study of the use of fluphenazine in the treatment of schizophrenic patients. Fifty patients (30 men and 20 women, 17 to 63 years of age) were given a mean dose of 12 mg p.o. daily of fluphenazine and were observed over a 70-day period. Fluphenazine was found to be most effective in paranoid and hebephrenic psychoses and least effective in more acute psychoses, perhaps because there is no injectable form of administration. Except

for extrapyramidal symptoms, tolerance to the drug was excellent, and its use is suggested as an initial treatment of most schizophrenic syndromes.

(No address)

937 Margat, P., Unal, I.; & Unal, J.
Essai de la trifluopérazine. (Study of trifluoperazine.) *Annales Médico-psychologiques*, 121(2):92-98, 1963.

The effects of trifluoperazine were noted in 15 patients with chronic delirium, paranoid psychosis, or hebephreno-catatonia. Treatment lasted from 30 to 150 days, and dosage progressed from 10 mg to 120 mg p.o. daily. Many side effects (including trembling, sleep disorder, paresthesia, and asthenia) were noted, which appear to be caused, not by dosage variation, but by individual sensitivities. Patients were evaluated according to the following four points: (1) behavior (six patients showed good results); (2) symptoms (three patients showed good results); (3) social, familial, and professional relations (six patients showed good results); and (4) M.M.P.I. rating (three patients showed good results). Trifluoperazine was found to have interesting antihallucinatory properties and noticeable possibilities in the area of social, familial, and professional relations.

Amiens, France

938 Dubarry, J. J., Tournerie, J., Marambat, G., & Auché, Y. **Expérimentation clinique de l'Optanox.** (Clinical trial of Optanox.) *Journal de Médecine de Bordeaux*, 8:1251-1256, 1963.

The use of 5-vinyl-5-(methyl butyl) alonylurea (Optanox) in the treatment of insomnia was tested in 36 inpatients suffering from insomnia before or during admission to the hospital. Treatment was about 7 days for each form of the drug: 0.10 g or 0.20 g, either p.o. or in suppository form. Patients were observed for time of drug administration, time of onset of sleep, duration of sleep, quality of sleep, and their state upon waking and throughout the morning. Blood and urine analyses were included in the trial. Of the 36 patients, 10 showed excellent results and 10 showed good results. A dosage of 0.10 g is suggested for occasional insomnia, and 0.20 g

is suggested for sleepless persons who habitually take sedatives. In only four cases were side effects noted; they included matinal cephal, dry mouth, and drowsiness.

Travail de la Clinique des Maladies de l'Appareil digestif de l'Hôpital Saint-André
Bordeaux, France

1939 Géraud, J., Gayral, L., Mouton, P., Candébat, L., & Roux, G. **Notes sur l'emploi de la trimépropimine (surmontil) pour le traitement de la dépression et de la mélancolie.** (Use of trimpropimine (surmontil) in the treatment of depression and melancholy.) *Annales Médico-Psychologiques*, 120(2):258-262, 1963.

Trimpropimine was tested in 49 patients with various forms of depression and melancholy. Dosage was administered 100 to 250 mg/day p.o. in less severe illness and by injection in more severe forms. Duration of treatment was 3 to 10 weeks, and associated treatment included thioridazine, levomepromazine, amobarbital, and ECT. Results showed 17 cures, 18 improvements, and 14 failures. It was indicated that psychoneuropathic conditions were most sensitive to trimpropimine treatment and that associated ECT treatment was generally beneficial. The only important side effects were cardiovascular: hypotension with bradycardia or tachycardia especially in older patients. It was concluded that treatment with trimpropimine is valuable therapy for depression and melancholy.

Clinique Neuro-Psychiatrique de la Faculté de Toulouse
Toulouse, France

1940 Jonas, P. **Esucos (U.C.B.3412).** *Acta Neurologica et Psychiatrica Belgica*, 61:774-775, 1963.

The author relates briefly his experience with dixyrazine. Administering the drug at first for its tranquilizing effect, he discovered that its side effects always included appetite increase and weight gain. Dixyrazine was then given to 50 patients with pathological thinness in dosages between 20 and 40 mg/day, and remarkable anabolic effects were obtained in all cases treated.

(No address)

CLINICAL STUDIES 1941-1945

- 1941 Kaivers, R. **Esucos (U.C.B. 3412).**
Acta Neurologica et Psychiatrica
Belgica, 61:771-773, 1963.

The effects of dixyrazine were observed in 19 outpatients (10 females and 9 males) with digestive disorders, in most cases of psychic origin. Dixyrazine was administered only after insufficient results were obtained with tranquilizers, sedatives, antispasmodics, and antiulcer agents. Dosage varied from 20 to 75 mg/day, and most patients were unaware of the nature of the agent they were receiving. Favorable results were obtained in 14 of the 19 patients, and the only side effect noted was drowsiness.

29 rue Marechal Gérard
Antwerp, Belgium

- 1942 Capone, Antonio & Holmberg, Marjorie.
Day care for alcoholics in acute withdrawal. Rhode Island Medical Journal, 46:532-535, 1963.

A system of day-care for patients in acute alcoholic withdrawal is described as a practical solution to the problem of giving adequate treatment to the alcoholic during the withdrawal crisis, in spite of the limited facilities. This system of treatment (usually 3 days) provides the patient with a bed, meals and medication in a day ward room 8:30 A.M. to 4:30 P.M. The medication, chlordiazepoxide, is given in the following dosage schedules: on admission day, 100 mg i.m. followed by 50 mg every 4 hours for four doses; on the second day, 25 mg p.o. every 4 hours for four doses, plus 50 mg at bedtime; on the third day, 10 mg p.o. every 4 hours for four doses. Of 166 patients who received chlordiazepoxide therapy, 109 completed the full 3 days. A total of 136 three-day courses was completed due to readmissions, and the clinical findings in these patients (89 males, 20 females) are reported. About 90% obtained good to excellent results from the 3-day treatment. Side effects (lethargy, fatigue, weakness, and dizziness), reported by nine patients, were corrected by decreasing the dose from 25 mg to 10 mg. Of the 25 patients who have maintained regular visits to the clinic for 6 months to a year, only 8 still require medication.

Department of Social Welfare
Providence, Rhode Island

- 1943 Selzer, Melvin L. **Alcoholism: Diagnosis and long range treatment.**
Michigan Medical Society, 62:980-983, 1963.

The diagnosis of alcoholism, as well as the treatment and hospitalization of the alcoholic are discussed. Alcoholism is extremely difficult to diagnose due to the patient's denial of being an alcoholic, and the ambivalence of the physician about alcoholism may cause him to support the patient's denial. Counseling and the use of family and friends as "therapeutic assistants" are the backbone of any treatment program. Chemical deterrents and tranquilizers may be used in treatment, and hospitalization for several weeks is often necessary for the treatment process to begin.

Ann Arbor, Michigan

- 1944 Greenhouse, H. Robert. **Report of a clinical trial of the use of hydroxyzine pamoate in the treatment of alcoholism.** Medical Times, 91(11):1069-1073, 1963.

Hydroxyzine pamoate was evaluated for relief of postalcoholic syndrome and for drug safety in 52 chronic alcoholic patients. Each patient received 50 mg hydroxyzine pamoate q.i.d., and were observed at weekly intervals. In order to determine the degree of relief, a checklist of the following significant symptoms of alcoholism was used: psychomotor agitation, anxiety, irritability, craving, insomnia, depression, anorexia, nausea, gastrointestinal distress, tension and alcoholic state. By the second visit, there was a 59% improvement; by the third visit, a 74% improvement; and by the fourth visit, a 75% improvement. Anxiety and irritability seemed to be the most effectively relieved symptoms. In the followup of 27 of the 52 patients, 18 remained sober for 6 to 23 months. No evidence of drug toxicity or habituation was observed.

Hamden, Connecticut

- 1945 Schildkraut, Joseph J., Klerman, Gerald L., Friend, Dale G., & Greenblatt, Milton. **Biochemical and pressor effects of oral D,L-dihydroxyphenylalanine in patients pretreated with antidepressant drugs.** Annals of the New York Academy of Sciences, 107:1005-1015, 1963.

The preliminary findings of studies of the concentration of catecholamines and the associated blood pressure changes following

the oral administration of *d,l*-dihydroxy-phenylalanine (*d,l*-DOPA) in patients pretreated with imipramine or the MAO inhibitor phenelzine are reported. Data were obtained on four female patients (30 to 65 years of age) with depressive illness (two of whom had been studied under placebo conditions) and three following phenelzine (45 to 60 mg/day for 3 weeks) pretreatment, and one following imipramine (150 mg/day for 3 weeks) pretreatment. The *d,l*-DOPA was administered in single doses of 50 to 200 mg orally. A twofold to threefold elevation of plasma catecholamines and a transitory elevation of blood pressure occurred in the patients pretreated with phenelzine. A similar elevation of plasma catecholamines was observed in the patients pretreated with imipramine, but a pressor response was not observed. No elevation of catecholamines or blood pressure occurred under placebo conditions. These results suggest that the elevation of plasma catecholamines is not a sufficient condition for the occurrence of a pressor response.

Harvard Medical School
Boston, Massachusetts

1946 Donnini, Luigi, Ignesti, Carlo, & Ciampi, Giampiero. *Ricerche sulla funzionalità epatica in schizofrenici prima e dopo trattamento con clorpromazina.* (Investigation of liver function in schizophrenics before and after chlorpromazine therapy.) *Fegato*, 8:155-169, 1963.

Liver-function studies were made on 54 chronic schizophrenic women, ranging in age from 17 to 74 years. The patients were divided into three groups: (1) 14 patients who had not received any promazine-type treatment; (2) 20 patients who had received chlorpromazine (150 mg/day p.o.) for at least 4 months; and (3) 20 patients who were receiving both chlorpromazine and choline hydrochloride (60 cg/day). Determinations included serum colloidal lability, total blood protein, alkaline phosphatase, acetylcholinesterase, SGOT and SGPT, amylase, and bilirubin. In the first group, an alteration of the protein crasis was characterized by a decrease of albumin and an increase of α_2 and γ globulins. In the second group, the colloidal lability reactions were frequently positive, and the enzyme levels were generally normal. After chlorpromazine therapy, a slight, but significant, improvement of these alterations was noted. The

addition of choline hydrochloride potentiated the protein crasis effects of chlorpromazine.

Institute of General Medicine
University of Florence
Florence, Italy

1947 Colao, G. & Scardino, R. *Sperimentazione clinica di un nuovo derivato della serie fenotiazinica (butirrilperazina) in medicina generale.* (Clinical trial of a new phenothiazine derivative (butyrylperazine) in general medicine.) *Riforma Medica*, 77:564-566, 1963.

Butyrylperazine, (Megalectyl), a new phenothiazine derivative, was used to treat 70 patients (36 males and 34 females) who were suffering from diverse disorders, with emesis as a common symptom. Diagnostic classification was as follows: anxiety 27, spastic intestinal disorder 19, disorders of pregnancy 12, X-radiation sickness 8, Hodgkin's disease 2, cerebral hemorrhage 1, and ictus 1. Daily dosage was one to two 1-mg tablets or four to six 2.5-mg suppositories. Butyrylperazine, by its neuroleptic action, was found to be useful as an antiemetic, anxiolytic, and enteric antispasmodic. The drug was particularly helpful in alleviating X-radiation sickness, enabling the patients to complete their course of roentgen therapy.

S. Gennaro Hospital
Naples, Italy

1948 Denzel, H. Alfred. *Fluphenazine in the treatment of psychotic patients.* *Journal of Clinical and Experimental Psychopathology and Quarterly Review of Psychiatry and Neurology*, 22(1):34-37, 1961.

Experiments were performed to determine the clinical efficacy, potency, and toxicity of fluphenazine and the feasibility of injecting the drug i.v. Fifty-one patients (27 females and 24 males, 17 to 68 years of age), including hyperactive, acutely psychotic patients and some depressed patients, were given doses of fluphenazine, ranging from 1 to 120 mg one to three times a day by tablet, elixir, or injection. Eight patients showed marked improvement, 19 moderate improvement, and 13 slight improvement; 12 patients were therapeutic failures. The best response was achieved in hyperactive patients, and the poorest response was in

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hypoactive, depressed patients. Intravenous administration, under carefully controlled conditions, provided a rapid method for establishing effective dosage and eliminating those patients in whom the ratio of therapeutic response to encountered risk or side effect would be unfavorable. Two case histories were given, illustrating a poor and a good response to i.v. fluphenazine. A high incidence (41%) of extrapyramidal reactions occurred. The incidence of other side effects is tabulated. Results obtained in three patients with delirium tremens were encouraging.

Winnebago State Hospital
Winnebago, Wisconsin

1949 Chatterji, N. N. **Psychopharmacology of imipramine.** Journal of the Indian Medical Association, 41:73-76, 1963.

The effects of imipramine were studied in 48 patients suffering from depressive illness. Imipramine dosage was 75 mg/kg p.o. initially, increasing at 3-day intervals until an effective dose was reached; the maximum dose varied from 75 to 300 mg/day. Duration of treatment ranged from 1 month and 7 days to 6 months. Imipramine was most effective in treating the manic-depressive and periodic-depressive groups. No toxic effects were noted. Side effects included weakness, tremors, dizziness, dry mouth, constipation, and hypotension. Certain patients were selected for study of the psychodynamic changes produced by imipramine. Reports are given of changes occurring in free-association sessions.

Lumbine Park Mental Hospital
Calcutta, India

1950 Janeczek, James, Sletten, Ivan, & Schiele, Burtrum C. **A pilot study with MA 568.** Psychopharmacology Service Center Bulletin, 2:106-108, 1963.

A 3-week pilot study of 4-(1-phenyl-4-piperazinyl)-butyl-3,4, 5-trimethoxybenzoate HCL (MA 568) was performed in 16 psychiatric patients with the following diagnosis: obsessive-compulsive reaction (2 patients), depressive states (5), manic-depressive manic reaction (1), and schizophrenic reaction (6 agitated and 2 withdrawn). Drug dosage was 100 mg b.i.d. initially, increasing to 300 mg q.i.d. by the end of the study. The two patients with obsessive-compulsive reaction did not improve, and one of them committed suicide. Three of

the depressed patients seemed worse on the medication. The two withdrawn schizophrenics showed no improvement. Two agitated schizophrenics showed some improvement, and one showed marked improvement. No serious side effects were noted. It was found that the dosage could be increased 400 mg/day without ill effects. The compound is not recommended for depressed patients.

University of Minnesota Hospital
Minneapolis, Minnesota

1951 Hausner, M. & Dolezal, V. **Group and individual psychotherapy under LSD.** Acta Psychotherapeutica et Psychosomatica, 11:39-59, 1963.

A study was made of various methods of individual and group psychotherapy using LSD. Results from the following experimental situations were compared: (1) Seven patients housed at a rehabilitation center for neurotics were given single injections of LSD (100 mg) at individual psychotherapeutic sessions. (2) Seven patients housed at the center received LSD (50 gamma) at a group psychotherapeutic session. (3) Four outpatients received LSD at individual psychotherapeutic sessions. (4) Five patients received placebo and 16 received no medication during psychotherapy. LSD was given in doses of 100µg for individual sessions and 50µg for group sessions. The most favorable results were obtained with a combination of individual LSD sessions and residence at the rehabilitation center. Social life with other neurotic patients at the center offered the patient an immediate practical situation in which to verify, intensify, and correct his new insight acquired from the LSD experience. LSD appeared to accelerate progress in the psychotherapeutic process. It was concluded, however, that LSD can never become a systematic psychotherapeutic agent.

Charles University
Prague, Czechoslovakia

1952 Levy, Howard A., Bodi, Tibor, Siegler, Peter E., Slap, Joseph, & Nodine, John H. **Chlorprothixene: A new non-phenothiazine ataractic agent: Spect in the outpatient therapy of psychoneuroses** Journal of Neuropsychiatry, 5(2):138-142, 1963.

The effectiveness of chlorprothixene was compared with that of fluphenazine, phenobarbital, and placebo in 158 outpatients

with various psychiatric disorders. Fifty-seven patients (including 19 male alcoholics, 25 to 63 years of age) received chlorprothixene (20 to 200 mg daily), 40 received fluphenazine (0.25 to 1.0 mg daily), 33 received phenobarbital (60 to 160 mg daily), and 28 received placebo (2 to 8 capsules daily). Data on the 19 alcoholics are presented separately. In the alcoholic group, all but two showed improvement on chlorprothixene. Chlorprothixene, fluphenazine, and phenobarbital produced improvement in 64%, 73%, and 58% of the neurotic patients, respectively. All three drugs were significantly superior to placebo. Side effects from chlorprothixene were as follows: drowsiness (7 cases), anorexia (4), nausea (2), tiredness (2), and pruritic rash (1). The use of individual dose adjustment in tranquilizer studies is emphasized because of variability of response to a fixed dose by patients suffering from a variety of clinical conditions.

Hahnemann Medical College
Philadelphia, Pennsylvania

1953 Grant, Alan P. **Isocarboxazid (Marplan) in the treatment of angina pectoris.** *American Heart Journal*, 65(1): 137-138, 1963.

The results obtained from two previous control trials in which isocarboxazid and a placebo were used in the treatment of angina pectoris are reviewed. It is concluded that isocarboxazid has some apparent analgesic effect in angina, even though the two trials differ as to the number of patients benefited, and in the second trial no significant difference was found between isocarboxazid and the placebo.

Belfast City Hospital
Belfast, Ireland

1954 Heine, B. E. & Turner, Paul. **Clinical trial of a new appetite suppressant drug.** *British Journal of Clinical Practice*, 17(9):529-531, 1963.

Clinical assessment of a new appetite suppressant, Filon, containing a mixture of benmetrazine-theoclate and phenbutrazate, is described in two studies, a pilot study and double-blind trial. Patients in both studies were followed for 3 months. The pilot study consisted of 12 obese patients, who were instructed to take a 1,000 calorie diet and given 1 tablet of Filon t.i.d. before meals. Five of the patients lost

more than 5% of their initial weight on this regimen. Appetite suppression became less marked with time. Only one of the five diabetics showed a rise in blood sugar level while on the drug. No significant changes were observed in the laboratory examination. Two complained of side effects—nausea and excessive thirst. Eleven patients were used in the double-blind trial and six on a 1,000 calorie diet alone served as controls. The same procedures were used for this study as the pilot study. There was less weight loss in the patients on the diet and placebo than those on diet alone, suggesting the nonadherence of the placebo group to the 1,000 calorie diet. Patients taking Filon kept to their diet. Appetite suppression diminished after the first 6 weeks (12 weeks total trial period). One hypertensive patient showed an increase in blood pressure after taking the drug. Thirst appeared to be the only side effect.

Edgware General Hospital
Middlesex, England

1955 Kent, Louise R. **The use of tranquilizers in the treatment of stuttering.** *Journal of Speech and Hearing Disorders*, 28(3):288-294, 1963.

A brief review is given of reports on the clinical and experimental use of the tranquilizers reserpine, chlorpromazine, meprobamate, and hydroxyzine in the treatment of stuttering. Generally, stutterers respond to the drugs in the same manner as nonstutterers. There is no evidence that any tranquilizer in any of the dosages used results in a statistically significant reduction in stuttering, either without speech therapy or as an adjunct to speech therapy.

University of Iowa
Iowa City, Iowa

1956 Tim, H. **Treatment of Parkinson syndrome with Trofranil.** *Brain and Nerve*, 13:391-936, 1961.

A discussion is given of the areas of brain activity in Parkinson's syndrome and the chemical composition and reactions of chlorpromazine, imipramine, and promazine. The drug trihexyphenidyl is used in combination with imipramine or by itself. In a clinical study, the authors administered imipramine alone or with trihexyphenidyl to eight cases of severe Parkinson syndrome, of which six

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responded favorably. Imipramine proved to be particularly effective in extremely depressive cases, with improvement in emotion and initiative, as well as a decrease in muscle rigidity. It seems to be more effective than trihexyphenidyl against Parkinson syndromes and is better tolerated. The drug effect is of symptomatic nature.

National Taiwan University
Taipei, Taiwan

1957 Shaffer, John W. **Chlordiazepoxide (Librium) and acquiescent response set.** *Psychological Reports*, 13:463-465, 1963.

The hypothesis that patients treated with chlordiazepoxide will attain higher scores on a measure of acquiescent response set (ARS) than will patients treated with placebo was tested using 93 white, male convalescing alcoholics (mean age, 45.6 years). During the 30-day double-blind study, the patients were given placebo (1 tablet, t.i.d.), chlordiazepoxide (10 mg t.i.d.), or chlordiazepoxide (20 mg t.i.d.). The measure of ARS, containing 42 heterogeneous items from the Minnesota Multiphasic Personality Inventory (MMPI), was given before and after treatment. The placebo group (31 patients) showed a nonsignificant mean decrease in acquiescence on retesting, whereas the groups receiving chlordiazepoxide (32 patients on 10 mg t.i.d. and 30 patients on 20 mg t.i.d.) showed mean increases in the same rank order as the dose of drug given. The hypothesis was supported by these results.

Spring Grove State Hospital
Baltimore, Maryland

1958 Mannarelli, A. A. **Propiomazine in presurgical regimens: Report of a 3-year trial.** *Journal of the American Osteopathic Association*, 62:913-916, 1963.

The presurgical anesthetic properties of propiomazine were compared with that of promethazine (previously used for a long period in presurgical programs) in a study of 141 patients (48 males and 93 females, 15 to 83 years of age) scheduled for various elective surgical procedures. Over a 3-year-period other agents administered with propiomazine included meperidine (50 mg i.m.), pentobarbital (90 mg), procaine amide (200 or 300 mg), and atropine sulfate (0.6 mg i.m.). Propiomazine was administered

in dosages ranging from 10 to 40 mg i.m., alone and in combination with the other drugs given. The combination of 40 mg propiomazine with 25 mg meperidine proved to be the most desirable in the majority of patients. This ratio of propiomazine produced calmness without interfering with quick return to normal consciousness, provided protection against undue physiologic stress without serious interference with cardiovascular or respiratory function, and suppressed nausea and vomiting to a degree equal to that observed with promethazine. The 40 mg dose of propiomazine combined with 25 mg meperidine was equal in antisecretory effect to promethazine with meperidine and atropine.

Kirksville College of Osteopathy and Surgery
Kirksville, Missouri

1959 Bojanovský, J., Chlouplová, K., & Horanská, D. **Srovnání účinku středních a vyšších dávek Meprobamatu při krátkodobém podávání. (Comparison of the effect of medium and higher doses of meprobamate administered for a short period.)** *Activita Nervosa Superior*, 5:225, 1963.

A study was made of 29 patients, including 26 females and 3 males, 20 to 61 years old. Their diagnoses included depressive neuroasthenia in 17, anxious neurosis in 4, obsessional neurosis in 2, hysteria in 1, hypochondriac neurosis in 1, and reactive depression in 4. Only patients who did not react to daily doses of placebo for 3 days were selected. The patients were divided into two equal groups. Placebo and drug were given in alternating 3-day periods. One group received 400 mg/day meprobamate in the first drug session and 800 mg/day in the second session, and the order of administration was reversed in the other group. Significant differences were obtained for the two groups. The group that began with the lower dose of meprobamate showed better results (Vinar ratio 2.71) than did the group beginning with the higher dose (Vinar ratio 1.65). However, the higher dose had distinctly better effect on anxiety and on sleep disorders. No substantial difference was found between dosages in regard to influence on depression, somatic disturbance or hypochondria. Side effects included drowsiness in 10 cases at the higher dose and in 1 case at the moderate dose. Upon administration of placebo between the two meprobamate doses, the condition of 20 of the patients worsened. Critical examination of individual reactivity to the different doses, based on patients showing improvement greater than 1.5 with one dose but no

improvement with the other dose, showed that individual reactivity did not play an important part in the experiment. The findings corroborate the hypothesis that if meprobamate is administered, it is better to give a large dose.

Military Hospital
Brno, Czechoslovakia

1960 Volmat, R., Beaudouin, J. L.,
Collin, J., Allers, G. & Vittouris, N.
Essais cliniques du neuroleptique 8909 RP (propériciazine) sur une population de malades chroniques internes. (Clinical trial of the neuroleptic RP 8909 (propericiazine) on chronic psychiatric inpatients.) Gazette Medicale de France, 70:1747-1760, 1963.

Propericiazine was tested in 32 female inpatients with chronic disorders, including depression, schizophrenia, delirium, and epilepsy. Intellectual deterioration was ascertained in one-third of the patients. The drug was administered p.o. 160 mg, usually t.i.d., and the results were as follows: favorable, 7 patients; slight, 12 patients; no change, 12 patients; and aggravated condition, 1 patient. Side effects included hypotension, asthenia, drowsiness, anorexia, and weight loss. Individual cases are presented, and results are examined according to the nature of the condition. It was concluded that propericiazine is not a major neuroleptic, but has important positive effects on character and behavior problems.

Clinique Universitaire de Neurologie et Psychiatrie de l'Ecole Nationale de Médecine et de Pharmacie de Besançon
Besançon, France

1961 Duchesnay, G. *Incidences thérapeutiques sur la glande mammaire, II^e partie. Galactorrhées. (Therapeutic accidents affecting the mammary gland. Part II. Galactorrhées.)* Cahiers R. M. F., 77:251-252, 1963.

A general discussion is presented of galactorrhea caused by neuroplegic medication. It has been found that reserpine and neuroleptic phenothiazines may cause galactorrhea, probably as a result of a disturbance of hypophyseal stimulin secretion. The dangers of galactorrhea include undesirable endocrine disturbance, psychological problems, and hyperproduction of prolactin in women at the ages when breast tumors frequently occur. It is suggested, therefore,

that when a galactorrhea appears in the course of neuroplegic treatment, treatment be discontinued. If discontinuation is impossible, antiprolactins should be administered in addition to the neuroplegic.

(No address)

1962 Eisenberg, Leon. *Drug therapy of overactivity in children. (Brief summary of remarks.)* Clinical Proceedings of the Children's Hospital, 19:253-255, 1963.

Drug therapy in the treatment of hyperkinesis in children is reviewed. There has been clinical success with dextroamphetamine in the treatment of hyperkinesis, beginning with a dosage of 5 mg and gradually increasing the dosage to 40 mg. The only side effect encountered with dextroamphetamine has been loss of weight, which usually could be controlled by adjusting the dose level. Methylphenidate, in doses ranging from 10 to 80 mg, has also been successful in the treatment of hyperkinesis. Meprobamate, perchlorperazine, and perphenazine have proved no better than placebo in the treatment of hyperkinesis, and should not be used because of their toxicity. If a phenothiazine is to be used in treating a child, chlorpromazine is the preferable drug because of its lower toxicity.

The Johns Hopkins School of Medicine
Baltimore, Maryland

1963 Parkhouse, James. *Placebo reactor.* Nature, 199(4890):308, 1963.

This paper reviews some of the concepts and ideas concerning "placebo reactors," and presents clinical findings in a study of postoperative pain control with morphine and placebo (normal saline). In the morphine--placebo trial, using an arbitrary pain score, only 3 out of 21 patients failed to achieve an improvement of at least one grade after morphine, whereas 8 of 18 patients were relieved by saline. When the ability to move and to cough were taken into account in evaluating pain, an improvement of one grade or more was achieved by 19 patients after morphine and by 9 after placebo, whereas an improvement of two or more grades was obtained by 10 of the 21 morphine cases and by none of those who had saline. Finally, an indication of the painfulness of deep breathing and coughing was obtained by measuring vital capacity and peak expiratory flow rate. The vital capacity improved in 10 of 12 patients

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after morphine, and in 2 of 9 after saline; peak expiratory flow rate improved in 4 of 12 cases given morphine and in 1 of 8 given saline. All this makes it difficult to understand how so-called "placebo reactors" can reliably be identified and excluded from a clinical trial, and how the "true" effect of the drug can be dissociated from its psychological effect.

Nuffield Department of Anesthetics
University of Oxford
Oxford, England

1964 Rider, J. Alfred & Moeller, Hugo C.
Double-blind evaluation of the use
of phentermine in treating obesity.
Applied Therapeutics, 5:523-524, 1963.

Comparable therapeutic effects of phentermine, an appetite depressant, in dosages of 4 to 8 mg t.i.d. or one 24-mg tablet daily (combined form of 8 mg immediate release and 16 mg sustained release) were studied in 31 obese patients (4 males and 27 females) between the ages of 24 and 75 years. Each patient took phentermine for 2 weeks and a placebo for 2 weeks. The patients were followed during 35 courses of placebo and 35 courses of treatment with the 25-mg tablet. There was a significant weight loss in the patients on phentermine and a 1,000 calorie daily diet. Those on the placebo and the 1,000 calorie diet did lose weight, but not as much as the drug group. The results were slightly better than for those in the 8 mg t.i.d. study. The side effects reported were jitters and insomnia.

University of California
Berkeley, California

See also: 1884, 1888, 1889, 1891, 1892,
1898, 1899, 1900, 1901, 1904, 1905, 1909,
1995, 1996, 2029

SIDE EFFECTS

1965 Kelly, H. Garfield, Fay, J. E., & Lavery, S. G. **Thioridazine hydrochloride (Mellaril): Its effect on the electrocardiogram and a report of two fatalities with electrocardiographic abnormalities.** Canadian Medical Association Journal, 89:546-554, 1963.

This report describes the effect of thioridazine in the ECG patterns of 28 hospitalized patients with major psychoses. The ECG patterns depict a quinidine-like effect of thioridazine on ventricular repolarization, in doses as low as 200 mg/day; the T waves have been found to flatten out and sometimes invert, and occasionally S-T segments have become convex and U waves have appeared. Two cases, one a 46-year-old woman with severe behavioral disorder following postvaccinal encephalitis, and the other, a 51-year-old woman with catatonic schizophrenia, are reported as patients who died while receiving large doses of thioridazine, 1,500 and 3,600 mg daily. Terminal ECG patterns in each instance were those of heart block, alternating with episodes of ventricular tachycardia. The myocardium of one of the fatal cases revealed edema, increased vascularity, and some increase in connective tissue elements, along with fragmentation of muscle fibers. These changes were most pronounced in the interventricular septum. Because of the quinidine-like action of thioridazine on ventricular repolarization, caution is indicated when it is administered in large doses.

Queen's University
Kingston, Ontario, Canada

1966 Niesenbaum, Leonard & Young, Irving. **Selective cerebellar granular layer degeneration: A nonspecific pathological finding in toxic states.** Journal of the Albert Einstein Medical Center, 11:234-237, 1963.

Two cases documenting the lack of specificity of cerebellar granular layer degeneration and its occurrence under other circumstances and in the absence of chronic

alcoholism are reported. A 50-year-old woman developed a severe generalized systemic reaction to meprobamate. She was treated with steroids and antihistamines, but developed toxicity, renal failure, gastrointestinal hemorrhage, and died 7 days later. Postmortem examination of the woman revealed a diffuse vasculitis, cerebral edema, cerebral vascular endothelial proliferation, and a fragmentation degeneration of the granular layer of the cerebellum. A 79-year-old-diabetic man, treated with protamine zinc insulin was hospitalized for lymphosarcoma. After three cobalt treatments, the patient died. Pathological examination revealed a fragmentation degeneration of the granular layer of the cerebellum. Both patients were so ill terminally that neurological evaluation was impossible, and neither patient had exhibited neurological abnormalities at the time of admission. The diversity of circumstances under which the cerebellar granular cell degeneration occurs indicates that it represents a manifestation of some severe toxic or agonal state to which these cells are particularly sensitive.

1319 West Tabor Road
Philadelphia 41, Pennsylvania

1967 Nørredam, Kai. **Chlorpromazine jaundice of long duration.** Acta Medica Scandinavica, 174(2):163-170, 1963.

The clinical, biochemical, and histological findings in two female patients with prolonged chlorpromazine jaundice are described. The patients, 35 and 37 years of age, were treated for paranoid symptoms with chlorpromazine 500 mg and 225 mg daily, respectively. The medication was stopped after 18 days in the case of the 37-year-old woman, and in 7 days with the 35-year-old woman due to chlorpromazine-induced jaundice. The jaundice lasted 19 months in the 37-year-old patient and 15 months in the 35-year-old patient. The 37-year-old patient developed diffuse xanthosis and xanthomas of the bones. Both patients presented highly elevated values of bilirubin, alkaline phosphatase,

SIDE EFFECTS 1968-1970

and transaminase in serum. Repeated histological examinations of liver tissue showed intrahepatic cholestasis, scattered necroses, and inflammatory infiltration of the portal areas. The latter tended to infiltrate the surrounding parenchyma, imitating the early stage of primary, biliary cirrhosis. Clinically, the disease showed complete spontaneous remission. However, months later, both patients still had biochemical signs of hepatic dysfunction, and showed slight to moderate fibrosis of the liver. The ultimate prognosis of the disease, especially as to the hepatic fibrosis, is not known.

Nordland County Hospital
Bodo, Norway

1968 Sirnes, Tollak B. Drug induced extrapyramidal reactions. *Acta Neurologica Scandinavica*, 39:209-217, 1963.

Parkinsonian syndrome and other extrapyramidal reactions have been found in all four of the major groups of neuroleptics---the phenothiazines, the thioxanthene derivatives, the reserpine derivatives, and haloperidol. The type and frequency of the extrapyramidal reactions vary with the various drug groups and between each drug within the same group. Examples are given of drugs in each of the four groups that do or do not produce extrapyramidal symptoms. Thioproperazine is discussed in detail, since it is the most potent and most extensively studied neuroleptic drug and induces a multitude of extrapyramidal reactions. Following doses of 5 to 50 mg/day, neurological disturbances begin to appear within 4 to 42 hours. The akinetic state is the first to appear, followed by the akinetic-hypertonic state, and the hyperkineto-hypertonic state (muscle hypertonia appears usually after 60 to 90 mg of the drug). Various abnormal muscular movements were observed, and modifications of the tendon reflexes were found in all patients within a few hours after receiving the first dose. Akathisia affected about 50% of the patients, but sensory disturbances were not common. Symptoms similar to those observed in epidemic encephalitis were seen. Factors influencing the type and frequency of extrapyramidal symptoms include dosage, sex difference, and brain injury. Age does not appear to be related to drug-induced parkinsonism. Mechanisms of drug action are discussed.

Department II
Kikemark Hospital
Asker, Norway

1969 Sunshine, Irving & Baumler, James. A fatal case of poisoning with amitriptyline. *Nature*, 199(4898):1103-1104, 1963.

A fatal case of amitriptyline poisoning is reported, and two methods (Stas-Otto procedure and direct chloroform extraction of white particulate matter samples) for isolating and detecting the drug are described. A 25-year-old man, who had made two unsuccessful suicide attempts over a 3-year period prior to treatment, was prescribed amitriptyline and other drugs. In the 6 months before his death, he was prescribed amitriptyline only. Immediately following his unexpected death, an empty bottle, which had contained 50 to 100 tablets (25 mg) of amitriptyline, was found empty in his room. Postmortem examination revealed no abnormalities, except for a full stomach containing undigested food and some white particulate matter, which was later identified chemically as amitriptyline. Both methods were applied to samples of blood, stomach content, liver, kidney, brain, and urine. When the direct-extraction procedure was applied to unhydrolyzed samples, no significant amounts of drug were detected. Results from both procedures indicate that the drug in the amount ingested is compatible with death, especially since, in this patient, there was no anatomical cause of death.

Western Reserve University
School of Medicine
Cleveland, Ohio

1970 Prasad, B. & Sinha, K. K. Acute muscular dystonias due to phenothiazines. *Journal of the Indian Medical Association*, 41:76-77, 1963.

Two cases of phenothiazine-induced acute muscular dystonias are reported. In the first case, a 37-year-old woman developed dyskinesia following a single dose of 5 mg trifluoperazine. The muscular spasms were controlled with 3 grains of phenobarbital sodium i.m. and 5 mg benzhexol HCl t.i.d. for 2 days. In the second case, a 29-year-old woman developed dyskinesia following her fourth injection of 40 mg trifluoperazine. She was given 200 mg phenobarbital and 50 mg promethazine, which controlled the spasms. The drug-induced dyskinetic syndrome is described, and the incidence in phenothiazine-treated patient exhibiting some form of extrapyramidal syndrome is reported.

Ranchi Medical College
Ranchi, India

SIDE EFFECTS 1971-1973

1971 Burgermeister, J. J., Dick, P., & Tissot, R. Effets de certains médicaments cataleptisants sur la motilité oculaire de malades atteints d'hébéphrénocatatonie. (Effects of certain drugs on ocular motility in hebephreno-catatonia.) Pathologie et Biologie, 11:445-454, 1963.

The effect of cataleptic drugs (thiopropazine, 10 mg; triperidol, 1.5 to 9 mg; and haloperidol, 9 mg) on the perceptive visual activity of nine patients with hebephreno-catatonia was observed. Perceptive visual activity (ocular movements), registered by an optical system during the exploration of the representation of geometric figures, was observed in five of the patients before and after medication, and observations on all patients were compared with those on controls. It was found that after medication with cataleptic agents, some of the pathological peculiarities observed before medication were increased: diminution of extent of movements, their fragmentation, and the number of sliding movements. In all cases, there was a disappearance or diminution of movements at the time of the visual representation. Clinical observation of the patients indicated that modification of ocular movement seems to be related to modifications in the general movements of the patient (akinesia and hyperkinesia, with fragmentation of movements) caused by the drug therapy.

clinique Psychiatrique de l'Université de Genève
Genève, Switzerland

1972 Chlorpromazine and convulsions.
British Medical Journal, 1(5344):
530, 1963.

Chlorpromazine may be used for the treatment of behavior disturbances in epileptic patients, but, when it is given for this purpose, the patient's dose of phenobarbital or other anticonvulsant drugs should not be reduced. With reduction, the risk of frequency of epileptic seizures is increased.

(to address)

1973 Crawford, J. P. Cheese dreams.
Lancet, 2:782, 1963. (Letter:
comment on letter by Dr. Asatoor et al.).

Comment is made on a letter (October 5 issue) concerning sympathomimetic amines in cheese. Due to the occurrence of these amines in cheese, the observation has been made that cheese, ingested at night, results in disturbed sleep.

Ide Hill
Kent, England

See also: 2034

BEHAVIORAL STUDIES

- 1974 Waller, Marcus B. & Morse, W. H.
Effects of pentobarbital on fixed-ratio reinforcement. *Journal of the Experimental Analysis of Behavior*, 6(1):125-130, 1963.

An experiment was conducted on 13 male, white Carneaux pigeons to determine the effects of pentobarbital on behavior maintained by a fixed-ratio schedule of 30 responses (FR 30). The pigeons were placed in an experimental chamber in which a dark period (15 minutes) was followed by a light period (10 minutes). The 30th peck on a blue light key produced a 3-second presentation of food. During the food presentation, the key light was extinguished, and the blue light appeared again at the end of food presentation with reinforcement of the 30th peck. Pentobarbital sodium was dissolved in 0.9% sodium chloride solution and injected i.m. immediately before the subject was put into the experimental chamber. Chlorpromazine HCl, methamphetamine HCl, and the sodium salt of 5-(1,3-dimethylbutyl)-5-ethyl barbituric acid (DMBE) were given in the same way. The doses specified are the total doses of these salts and were as follows: pentobarbital (2 to 5.6 mg), chlorpromazine (1 to 10 mg), methamphetamine (0.1 mg), and DMBE (0.1 to 1 mg). Certain doses of pentobarbital consistently increased the rate of pecking, whereas higher doses produced decrements in rate of responding. In 10 of 13 birds, 2 mg pentobarbital increased the rate of responding, 8 of 9 birds showed an increase at 3 mg, and 8 of 13 birds showed an increase at 5.6-mg dose. Chlorpromazine increased the response rate in 3 of 5 birds, and 0.1 mg methamphetamine increased the rate in 3 of 8 birds. The rate increased above the control level in only one of five birds given DMBE, and this did not exceed the increase produced with placebo (saline).

Harvard Medical School
 Boston, Massachusetts

- 1975 Kelleher, Robert T., Gill, Charles A., Riddle, William C., & Cook, Leonard
On the use of the squirrel monkey in behavioral and pharmacological experiments. *Journal of the Experimental Analysis of Behavior*, 6(2):249-252, 1963.

Observations are reported on techniques of handling, raising, and feeding squirrel monkeys that might be useful in behavioral or pharmacological experiments. An apparatus is described for restraining the monkey while drugs are administered parenterally. The animals are easily tamed and very tractable, and may be housed in groups without difficulty. Chronic food deprivation and experimental stresses may render the monkey more susceptible to illness. The squirrel monkey seems comparable to the Rhesus monkey in its performance on simple or multiple schedules of positive and negative reinforcement.

Smith, Kline and French Laboratories
 Philadelphia, Pennsylvania

- 1976 Mechner, Francis & Latranyi, Miklos
Behavioral effects of caffeine, methamphetamine, and methylphenidate in the rat. *Journal of the Experimental Analysis of Behavior*, 6(3):331-342, 1963.

Three widely used stimulant drugs, caffeine, methamphetamine, and methylphenidate, were compared in 32 male albino rats at four to five doses per drug under four different behavioral procedures. The apparatus used a rat rotor, a device which cycles rats through a testing station automatically and continuously. Three to six weeks of training were generally required before an animal's performance was sufficiently stable.

for the drug study to be undertaken. The range of dosage administered was: caffeine (2.5, 5.0, 15.0, 30.0, and 60 mg/kg), methamphetamine (0.2, 0.4, 0.8, 1.6, and 3.2 mg/kg), and methylphenidate (6.0, 12.0, 24.0, and 48.0 mg/kg). All treatments were completely crossed over and were administered in a random sequence over a 15-week period. The four behavioral procedures used were: (1) fixed interval, (2) fixed number, (3) fixed minimum interval, and (4) fixed consecutive number. Under the fixed-interval procedure, the percentage change in the number of responses to bar B per reinforcement was significantly smaller with caffeine than with methamphetamine or methylphenidate ($p < 0.001$). Under the fixed-interval procedure, the percentage change was significantly smaller with methamphetamine than with caffeine or methylphenidate ($p < 0.001$). Thus, methylphenidate had a methamphetamine-like effect under fixed interval and a caffeine-like effect under fixed number.

Basic Systems Incorporated
New York, New York

1977 Davis, Marvin W. & Nichols, John R.
A technique for self-injection of drugs in the study of reinforcement.
Journal of the Experimental Analysis of Behavior. 6(2):233-235, 1963.

An automatic apparatus for self-injection of drugs in the study of the reinforcing effects of drugs is described. The apparatus prevents undesirable handling or immobilization of the subject and enables repeated injections from a distance on a continuing basis in the unrestrained, freely active rat. The apparatus injects rapidly a predetermined volume of liquid upon the performance of an instrumental response by the experimental subject. Usefulness of this apparatus is evident in preliminary observations on lever pressing of pairs of either non-dependent or morphine-dependent rats (receiving 1.0 or 0.5 mg of morphine per injection). Applicability of this apparatus and technique to prolonged studies has been demonstrated by maintenance of rats in a continuing self-injection situation for as long as 50 days.

University of Oklahoma
Norman, Oklahoma

1978 Bindra, Dalbir & Anchel, Harvey.

Immobility as an avoidance response, and its disruption by drugs. *Journal of the Experimental Analysis of Behavior*, 6(2):213-218, 1963.

Three experiments were carried out to determine whether animals can learn to sit or stand motionless in order to escape or avoid electric shock. In Experiment I, 10 adult, male hooded rats (weighing 200 g) were used to ascertain if immobility, as an avoidance response to electric shock (0.75 ma), could be learned. The control animal received a shock regardless of what he was doing, but it occurred at the same time the experimental animal received a shock. The experimental animals received a shock when they walked, reared, sniffed, or were active in other ways. After all the experimental animals had learned the response and remained motionless as an avoidance response, four test sessions were set up to determine how far the observed immobility was a response to the specific training situation. The results indicated that immobility response in the experimental animals was not an unconditioned "freezing" response to electric shock, but a trained avoidance response. The responses, as a result of test sessions utilizing different situations, indicated that the response was specifically associated with the situation in which the animal was trained. Experiment II was designed to determine the relation between shock intensity (ranging from 0.50 to 2.65 ma) and the acquisition of the immobility response in four groups of male hooded rats (totaling 24) plus 6 controls. The results revealed that this response is more readily acquired at higher shock intensities. The effects of i.p. injections of methylphenidate (4 to 8 mg/kg), chlorpromazine (2 to 6 mg/kg), and imipramine (15 to 25 mg/kg) on the immobility avoidance response in 13 adult male hooded rats (weighing 200 g) were studied. Only one shock intensity, 0.75 ma, was used in the training. Rats were divided into two groups—Group L of five rats was given the lower drug doses and Group H of eight rats was given the higher doses. All three drugs produced a decrement in immobility, but the pattern and amount of the effects of the three drugs were quite different.

Department of Psychology
McGill University
Montreal 2, P.Q., Canada

- 1979 Sidley, N. A. & Schoenfeld, W. N.
Effects of chlorpromazine and *d*-amphetamine on escape and avoidance behavior under a temporally defined schedule of negative reinforcement. Journal of the Experimental Analysis of Behavior, 6(2):293-295, 1963.

The present study examines the effects of chlorpromazine and *d*-amphetamine on the behavior of two male albino rats under a temporally defined schedule of negative reinforcement. The apparatus used delivered a 1-milliampere polarity-scrambled shock to the feet of the 170-day-old animals through 16 stainless steel rods composing the grid floor. A response during a shock terminated that shock, and any response not in a time-out period, which occurred within 10 seconds before a scheduled shock had the effect of canceling that shock. The drugs were administered i.p. for 7 days in dosages ranging from 1.0 to 4.0 mg/kg chlorpromazine and 0.5 to 0.8 mg/kg *d*-amphetamine. The drugs were given 30 minutes before an experimental session; each session lasted either 100 or 150 minutes. Chlorpromazine has the effect of slowing the overall rate of responding, and the resulting greater number of shocks gives the appearance of a decrease in avoidance efficiency. The effect of *d*-amphetamine is to increase the rate of response, and thereby decrease the number of shocks delivered.

Columbia University
 New York, New York

- 1980 Polidora, V. J. **A sequential response method of studying complex behavior in animals and its application to the measurement of drug effects.** Journal of the Experimental Analysis of Behavior, 6(2):271-277, 1963.

A behavioral testing method is described that was developed for studying the effects in animals of hallucinogenic and other drugs having detrimental effects on complex behavior in man. The method requires the animal to respond in a certain sequence to four identical response sites spaced 90° apart within a cylindrical test compartment. After each subject learned to perform its one particular sequence within this environment, and the performance was stabilized, drug effects were then studied on a battery of such subjects whose sequential response habits represented a continuum of sequence complexity. Experiments on rats with JB 329, which is hallucinogenic in man, showed that the method yields quantitative measures of

detrimental behavioral effects in terms of dose-response and dose-time relationships, in addition to providing an estimate of the interactive effect between drug dose and behavioral complexity. It was found that for a given magnitude of behavioral detriment, drug dose and behavioral complexity of sequence were inversely related; that is, a given drug dose had a greater behavioral effect the more complex the sequence. An empirical ranking of response sequences along a functional behavioral complexity dimension is presented.

University of Wisconsin
 Primate Laboratories
 Madison, Wisconsin

- 1981 Brown, Hugh. ***d*-Amphetamine-chlorpromazine antagonism in a food reinforced operant.** Journal of the Experimental Analysis of Behavior, 6(3):395-398, 1963.

Dose-effect curves for the chlorpromazine antagonism of the amphetamine-induced repression of behavioral response were obtained with rats on a milk reinforced FR 10 schedule. Four male Wistar rats, 6-8 months of age, were trained to press a lever for milk reinforcement. A dose of *d*-amphetamine (2.5 mg/kg i.p.) that completely suppressed all responding for 60 minutes was administered simultaneously with various doses of chlorpromazine. The *d*-amphetamine induced cessation of responding was removed by several of the doses of chlorpromazine, with maximal antagonism occurring at a dose of 1.5 mg/kg i.p. This dose of chlorpromazine, when administered independently, produced no observable side effects and showed no effect on the FR 10 schedule. One animal appeared to develop tolerance to the repeated dosages of *d*-amphetamine.

University of Maryland
 College Park, Maryland

- 1982 Coppock, H. W., Meeks, W. A., & Huard, D. V. **Drug and strain effects on performance and reversal of a head-position habit.** Journal of Comparative and Physiological Psychology, 56(3):551-557, 1963.

A study using determinate reinforcement (shock termination) during evaluation of initial strength of response and also dur-

counterconditioning or reversal learning was carried out in order to determine what effects drugs have on responses acquired during each phase. The 112 male rats (230 to 300 g in weight) used in this study consisted of two varieties---56 were Sprague-Dawley albino rats that were docile, and the other 56 subjects were hooded rats of the Long-Evans strain that were extremely aggressive and resistant to restraint. The 112 subjects were randomly assigned in a factorial design to test the effects of seven drugs, two dosages, two strains, and no delays in reinforcement upon shock escape conditioning in a two-choice situation. The drugs used were meprobamate (ME) 10 mg/kg, chlorpromazine (CH) 6 mg/kg, morphine (MO) 5 and 15 mg/kg, pentobarbital sodium (PE) 12 and 22 mg/kg, amphetamine sulfate 0.5 and 1.5 mg/kg, and physiological saline. Mean rate of reversal learning (θ) was lowest under the drugs yielding the highest p during prereversal trials ($\theta = -0.61$) and during the intertrials ($\theta = -0.75$). The hooded rats in relation to the albino rats were characterized by fewer successes and higher threshold in prereversal learning and by a subsequently higher θ during reversal learning. The delay of reinforcement affected the asymptote but not the rate of reversal learning. There was a decrease in magnitude of the negative relationships between performance and rate of reversal learning. Chronic administration of CH and ME for eight days did not support the hypothesis that the prereversal strength and rate of reversal learning would be altered after multiple injections. Large, compared with small doses, produced a lower and increased the latency.

Arizona State University
Tempe, Arizona

3 Singer, Jerome E. Sympathetic activation, drugs, and fear. *Journal of Comparative and Physiological Psychology*, 53(3):612-615, 1963.

Twenty-two naive albino rats, 60 to 180 days of age, were used to study the effects of adrenalin (0.001 or 0.050 mg/kg i.p.), chlorpromazine (2.0 mg/kg i.p.), and placebo on emotional behavior, which was interpreted in terms of fear and nonfear. In the fear condition, noise and light stimuli were presented on prior to the observation period, and in the nonfear condition, the stimuli

were not used. The three groups were observed individually, and five responses noted---defecation, urination, variation in activity, trembling, and face washing. The ability of each response to differentiate fear conditions was tested by two-tailed t -tests. The unweighted standard scores for each response plus a constant score were combined to yield a single number referred to as the fright index. The adrenalin-treated subjects displayed more fright than did the placebo subjects, and the chlorpromazine-treated animals displayed the least. In the nonfearful situation, the drug groups manifested no differential fright. Thus, in a fear producing situation, the greater the drug-induced sympathetic arousal, the greater the amount of fright displayed.

Pennsylvania State University
University Park, Pennsylvania

1984 Poschel, P. H. Effects of methamphetamine on hunger and thirst motivated variable-interval performance. *Journal of Comparative and Physiological Psychology*, 56(6):968-973, 1963.

This experiment reassesses the motivational effects of methamphetamine on hunger- and thirst-motivated variable-interval performance and tests the hypothesis that amphetamines exert a dual effect on behavior. Fourteen male, albino Holtzman rats, 134 days old, were tested in two separate groups, one motivated by hunger, and the other by thirst, with all other conditions being equal. Two Skinner boxes were used to test a learned instrumental response and a consummatory response. Methamphetamine was administered in doses of 0.75, 1.50, and 2.25 mg/kg, and saline was given to the controls. Methamphetamine selectively depressed food-reinforced responding, the degree of depression depending on dose. Responding for water was increased at the doses used. On a second measure (percentage of reinforcers consumed of those earned), the hunger group also showed significantly lower scores than the thirst group. Results indicate that methamphetamine has a dual effect on behavior, causing an increase in motor stimulation and a decrease in hunger drive.

Parke, Davis Company
Ann Arbor, Michigan

- 1985 Young, Richard David. **Effect of prenatal maternal injection of epinephrine on postnatal offspring behavior.** *Journal of Comparative and Physiological Psychology*, 56(5):929-932, 1963.

This study was designed to explore the possible effect of daily maternal injections of epinephrine (0.5 mm/kg/day i.p. in a water solution) during the gestation period on the postnatal behavior of the offspring. The 12 pregnant Wistar rats were divided into four groups. Two groups received daily injections of epinephrine and saline. The third group was handled, and the fourth group had a normal pregnancy. Offspring were weaned and assigned to their experimental subgroup at 21 days of age. The performances of the offspring were evaluated in the open-field test and Hebb-Williams maze at 30 and 60 days of age. Epinephrine group offspring were highly emotional in the open-field test and had increased latency scores in the maze. There was no measurable difference in behavior among the saline, handling, and control groups. The results indicate the general hypothesis that prenatal factors have significant consequences for early postnatal behavior of offspring.

Indiana University
Bloomington, Indiana

- 1986 Doty, Larry A. & Doty, Barbara A. **Chlorpromazine-produced response decrements as a function of problem difficulty level.** *Journal of Comparative and Physiological Psychology*, 56(4):740-745, 1963.

This experiment is designed to study relationships between chlorpromazine-produced response deficits and problem-difficulty level under standardized conditions of experimental procedure and drug treatment. The subjects were 80 hooded rats of Long-Evans stock, equally divided between the sexes. They were 60 days old at the time of testing and were maintained on ad lib feeding and water schedules. Forty rats learned a simple avoidance, 40 others a discriminated avoidance. Each group was then subdivided, one-half being extinguished under drug, one-half with no drug. During both acquisition and extinction trials, drug-treated subjects received i.p. injections of 1.25 mg/kg chlorpromazine 2 hours prior to testing, and control subjects

received equal volume injections of saline solution. Chlorpromazine was found to suppress acquisition and facilitate extinction of avoidances for both problems. Results indicate that drug effects are a function of problem difficulty, with a powerful interaction appearing between effects of drug administration during extinction and acquisition as problem difficulty increases.

Northern Illinois University
De Kalb, Illinois

- 1987 Andrew, R. J. **Effect of testosterone on the behavior of the domestic chick.** *Journal of Comparative and Physiological Psychology*, 56(5):933-940, 1963.

The effect of testosterone was studied on the patterns of vocalization in young chick (*Gallus domesticus*). Chicks were of the Hall Sex-link strain, weighing 40 g at 2 days of age. Four experiments were performed; the number of experimental and control chicks and the injection schedules are tabulated for each experiment. Experimental chicks received 0.25 mg/20 g testosterone propionate or enanthate i.m. in sesame oil at each injection. Controls received corresponding amounts of sesame oil alone. In one experiment, 0.02 mg/20 g of mammalian estrone was given. Testosterone caused all the patterns of vocalization to develop higher intensity variants, which were longer, began at a higher pitch, and tended to be more fully trilled. Any pattern, once performed, tended to be repeated often, so that calls occurred in bouts instead of singly. Calls used in all the main functional systems of adult instinctive responses (e.g., aggressive, sexual, feeding, and alarm responses) were affected. The mechanism by which these new calls were produced appeared to depend on nonspecific facilitatory effect of testosterone on a single control system on which all vocalizations depend.

Yale University
New Haven, Connecticut

- 1988 Boullin, D. J. **Behaviour of rats depleted of 5-hydroxytryptamine by feeding a diet free of tryptophan.** *Psychopharmacologia*, 5(1):28-38, 1963.

In order to study the relationship of the behavioral changes to 5-hydroxytryptamine

(5HT) and also the effect of reserpine, 47 male, weanling, Sprague-Dawley rats were depleted of 5HT by feeding a synthetic diet free of tryptophan for 14 to 35 days. Control animals were fed an identical diet with the addition of 0.4% L-tryptophan in place of an equivalent amount of sodium bicarbonate. Rats were killed by decapitation, and 5HT was extracted from whole brain and from the mucosa of the small intestine. The tryptophan-free diet produced a severe depletion of 5HT levels both in the brain and intestine. Thirty-five out of the 47 deficient animals showed normal behavior for the first 2 weeks, but they then became hyperactive. Convulsions, backward circling, head nodding, tremor, ataxia, and squealing were specific behavioral changes that appeared after about 4 weeks. Normal behavior was not restored in three animals when given *DL*-5-hydroxytryptophan (70 mg/kg s.c.), but brain and intestinal mucosal 5HT levels were found to be elevated. Reserpine (1 mg/kg s.c.), given to 16 tryptophan-deficient, 6 normal, and 6 control rats, produced the signs associated with typical reserpine-sedation in the normals, and in 13 of the 16 tryptophan-deficient rats. When 5HT (70 µg/kg s.c.) was given after reserpine, convulsions reappeared within 1 hour, and no 5HT was detected in the brain assay. These findings suggest that the sedative effects of reserpine are unlikely to be due to changes in levels of free 5HT in the CNS.

Queen's College
Dundee, Scotland

1989 Jarrard, Leonard E. Effects of D-lysergic acid diethylamide on operant behavior in the rat. *Psychopharmacologia*, 5(1):39-46, 1963.

Experiments were performed to determine the dose-response and time-response relations for LSD and to compare the effects of different doses of the drug on behavior maintained by positive reinforcement with the effects on behavior maintained by negative reinforcement. Twelve male, albino rats (90 to 100 days old) were used. Half of the subjects were trained to press a bar for food on an aperiodic schedule, and half were trained with a Sidman-type avoidance procedure to press a bar to avoid shock. Each subject served as his own control and was

injected with a physiological saline solution, 0.05, 0.10, 0.20, 0.40, and 0.80 mg/kg of LSD-25. Treatments and conditioning situations were assigned according to a Latin-square design. In the food-reward situation, injection with LSD-25 (0.05 mg/kg) increased the number of bar presses emitted; doses of 0.20, 0.40, and 0.80 mg/kg decreased the number of responses. In the shock-avoidance situation, there was a decrease in the number of shocks received during the first 30 minutes when the subjects were treated with 0.05 mg/kg, but injections of 0.40 and 0.80 mg/kg resulted in more shocks during this time period. No significant differences in number of bar presses were found for any of the dosages. The effects of the drug were found to persist for approximately 1-1/2 hours following injection. The present results support an interpretation of central-stimulating and central-depressing effects of LSD-25, depending on the dose level.

Washington and Lee University
Lexington, Virginia

1990 Stratton, Lois O. & Petrinovich, Lewis. Post-trial injections of an anti-cholinesterase drug and maze learning in two strains of rats. *Psychopharmacologia*, 5(1):47-54, 1963.

This experiment tests the hypothesis that posttrial injections of physostigmine, a powerful anticholinesterase drug, will facilitate learning in the rat. The subjects were 86 rats of which 50 (59 to 64 days old) were Tryon maze brights (25 males and 25 females) and 36 (64 to 208 days old) were Tryon maze dulls (18 females and 18 males). Each of the maze brights was assigned to one of the following five groups: 10 animals in the control group receiving 1 cc/kg of the vehicle (distilled water and sodium bisulfate) and groups of 10 animals each, receiving 0.25, 0.50, 0.625, or 0.75 mg/kg of physostigmine salicylate in 1 cc/kg of the vehicle. The maze dulls were assigned to six groups: 6 animals in the control group and groups of 6 animals each, receiving 0.25, 0.50, 0.625, 0.75, or 1.00 mg/kg of physostigmine in 1 cc/kg of the vehicle. Daily trials in a Lashley III maze showed that the lowest dosage had no effect on learning but as the dosage increased, learning improved and was significantly better than that of control animals. The

optimal dosage for maze brights was 0.50 mg/kg, and that for maze dulls was 0.75 mg/kg. The highest dosages used (0.75 mg/kg for maze brights and 1.00 mg/kg for maze dulls) resulted in a disruption of performance. The perseveration--consolidation theory of memory was supported by this experiment. Evidence that learning efficiency is related to the acetylcholine--cholinesterase ratio in the rat brain was also proved.

Langley-Porter Neuropsychiatric Institute
San Francisco, California

1991 Wikler, Abraham., Martin, William R.,
Pescor, Frank T., & Eades, Charles G.
Factors regulating oral consumption of
opioid (etonitazene) by morphine-addicted
rats. *Psychopharmacologia*, 5:55-76, 1963.

As part of a long-term study on the possible roles of conditioning factors in the genesis of relapse to an opioid drug following apparent recovery from the withdrawal phenomena produced by the addicting agent, factors regulating the oral consumption of the opioid etonitazene were studied in morphine-addicted rats. Male, albino Wistar rats (5 months old, 416 to 521 g in weight) were used. The volumes and rates of water or etonitazene-solution consumption were measured in control (saline-treated) and addicted rats during the first 7 hours and the succeeding 17 hours after morning injections of saline or morphine. Activity, the frequencies of the "wet dog" abstinence syndrome, oxygen-consumption rates, and colonic temperatures were also measured. Etonitazene was used in concentrations of 5, 10, 20, or 40 μ /ml. Control animals drank water at a relatively low rate during the morning and early afternoon and at a faster rate from then until about 8 o'clock the next morning. Addicted animals showed very rapid rates of drinking from about 2 hours after the morning injection of morphine until about 13 to 14 hours after injection, when the drinking rates slowed markedly. The occurrence of the lower rate of drinking coincided with the earliest appearance of the abstinence syndrome. When the etonitazene solution was available instead of water, addicted rats consumed much larger volumes of the drug solution from 8 to 24 hours following injection than control animals. It was concluded that suppression of abstinence phenomena is the major factor regulating oral consumption of etonitazene in

dilute aqueous solutions by morphine-addicted rats and that the pharmacological properties of etonitazene and morphine are sufficiently similar to warrant use of etonitazene solutions in lieu of morphine solution as an oral reinforcing agent in studies on conditioning of opioid-acquisition behavior in this species.

National Institute of Mental Health
Addiction Research Center
Lexington, Kentucky

1992 Ordy, J. M., Latanick, A., Johnson,
R., & Massopust, L. C., Jr.
Chlorpromazine effects on pregnancy and
offspring in mice. *Proceedings of the
Society for Experimental Biology and
Medicine*, 113(4):833-836, 1963.

The purposes of this investigation were to obtain quantitative data on the effects of chronic chlorpromazine treatments in pregnant mice on delays between mating and litter birth, maternal debility as evidenced by weight and behavior changes, and drug effects on litter size and weight of offspring. Eighty inbred C57Bl/10 mice breeder pairs were mated and divided into four groups. Twenty female mice received 4 mg/kg p.o. and 20 females received 16 mg/kg p.o. of chlorpromazine throughout pregnancy, while the other two groups of 20 females each received corresponding volumes of placebo p.o. The gestation time for placebo rats was 22.35 days, for the low dose of chlorpromazine rats 23.85 days, and for the high dose rats 28.80 days. The mean litter size for the placebo group was 8.0 and the mean litter weight was 1.41 g. The litter size for the low dose of drug was 7.9 and the litter weight was 1.33 g, and for the high drug dosage, the litter size was 5.8 and litter weight was 1.17 g. There was no significant difference in maternal incremental weight changes. The 16 mg/kg dose level produced sedation for 1 to 5 hours, but there were no significant differences in behavior observed between placebo mothers and the low drug dosage mothers.

Cleveland Psychiatric Institute
Cleveland, Ohio

1993 Krivoy, William A., Lane, Montague, & Kroeger, Donald C. **Effects of drugs on the electric knife fish, *Eigenmannia virescens***. Proceedings of the Society for Experimental Biology and Medicine, 114(3): 640-644, 1963.

The results of studies on the effects of methylphenidate, pentylenetetrazole, phenobarbital, morphine, and nalorphine on the electric transparent knife fish *Eigenmannia virescens* are presented. Movement of the fish, contained in a 20-liter aquarium divided into two compartments, was measured by silver electrodes placed in the smaller compartment containing the fish. Changes in amplitude were recorded by another pair of silver electrodes placed in the larger compartment. All drugs were administered by pipetting them into the aquarium. Amplitude variation (AV) as a function of time was determined through information analysis of the electrical activities of the fish. Methylphenidate at 0.005 µg/ml of bath produced a 45% depression of AV and an 87% depression at 1.25 µg/ml, as recorded from amplitude-dependent electrodes. No consistent changes in AV were noted in potentials simultaneously recorded from movement-dependent electrodes. A 50% decrease in AV occurred at a concentration of 1.4 µg/ml of phenobarbital, but no changes were noted in AV recorded from movement-dependent electrodes. Morphine (0.45 µg/ml) added on 3 successive days depressed AV to 55% of control. For the next 3 days, 0.90 µg/ml was added, and then on the seventh day 2.35 µg/ml was added. The AV had increased to 83% of the control on day 1. Nalorphine (0.5 µg/ml) increased AV to 144% of the activity after the last morphine addition. Changes in AV recorded from movement-dependent electrodes paralleled those from amplitude-dependent electrodes, but they were less pronounced. Pentylenetetrazole (2.5 to 7.5 µg/ml) did not produce consistent changes from either set of electrodes. The data suggested that the fish developed tolerance to morphine, as well as physical dependence on the drug. This system appeared to be suitable as a bioassay technique.

Taylor University
Houston, Texas

1994 Gyermek, Laszlo & Sumi, Tadaaki. **Potentiating actions of indolealkylamines and lysergic acid diethylamide on**

reflexes elicited by 5-hydroxytryptamine. Proceedings of the Society for Experimental Biology and Medicine, 114(2):436-439, 1963.

The potentiating actions of some indolealkylamines and lysergic acid diethylamide (LSD) on the reflexes elicited by 5HT in cats under nembutal anesthesia (35 mg/kg i.p.) were investigated. The cardiovascular and respiratory reflex actions (blood-pressure fall, bradycardia, apnea) of 5HT (10 µg/kg to 40 µg/kg i.v.) were potentiated by tryptamine (0.4 mg/kg i.v.); *N,N*-diethyltryptamine (0.1 mg/kg i.v.); *N,N*-dipropyltryptamine; *N,N*-dibutyltryptamine; psilocin (0.4 mg/kg i.v.); and LSD (40 µg/kg and 100 µg/kg). Since these same agents potentiated the action on afferent vagal fibers activated by 5HT, it is proposed that the indolealkylamines and LSD influence 5HT reflexes by facilitating the stimulant action of 5HT on viscerosensory receptors.

Saint Elizabeths Hospital
Washington, D.C.

1995 Evans, Ray B. & Marmorston, Jessie. **Improved mental functioning with Premarin therapy in atherosclerosis.** Proceedings of the Society for Experimental Biology and Medicine, 113(3):698-703, 1963.

This report concerns the effect of Premarin, a water-soluble estrogen, on certain aspects of cognitive functioning, the hypothesis being that mental impairment decreases in patients with atherosclerosis treated with Premarin. An analysis was made of 101 patients, 51 who had cerebral thrombosis and 50 who had myocardial infarction. Of the 51 cerebral patients, 23 received Premarin and 28 received placebo. There were 25 cardiac patients on Premarin and 25 on placebo. There was a total of 10 women and 38 men on placebo, with ages ranging from 39 to 80 years. Each patient was given the Rorschach test at the time of assignment to treatment or shortly thereafter, and the test was repeated after 6 to 16 months of treatment, each patient serving as his own control. Relatively small doses of Premarin were administered orally, 0.625 mg daily for women and from 0.625 to 2.5 mg for men; most frequently, the dosage was 1.25 mg daily. The Rorschach tests were assessed for indications of impairment in thinking, and each patient received a score denoting amount of increase or decrease in impairment after treatment. There was a considerable overlap

in scores between Premarin and placebo patients, and gains were relatively small for individual patients. Nevertheless, improved mental functioning was found in both cerebral and cardiac patients treated with Premarin in comparison with those on placebo, and a positive association was observed between Premarin therapy and decreased mental impairment.

Loma Linda University
School of Medicine
Loma Linda, California

- 1996 Owen, John E., Jr. **Psychopharmacological studies of some 1-(chlorophenyl)-2-aminopropanes. I. Effects on appetitive-controlled behavior.** *Journal of Pharmaceutical Sciences*, 52(7):679-683, 1963.

The effects on appetitive-controlled behavior of a series of 1-phenyl-2-aminopropanes (1.0 to 8.0 mg/kg) with chloro substitutions on the 2,4, 3,4, and 4 positions on the phenyl ring and their optical isomers are compared with *dl*- and *d*-amphetamine (1.0 to 3.2 mg/kg) and methamphetamine (1.0 to 3.2 mg/kg) on an FR (fixed-ratio) schedule for food reinforcement. Wistar-strain rats, initially weighing 400 to 450 g, were used. They were trained to press a lever 30 times in order to receive 0.25 ml of sweetened condensed milk. Thirty minutes after drug administration, each rat was given a session consisting of 40 reinforcements. Two variables of this appetitive-controlled FR behavior were studied—the running response rates and the total time used to complete each session. With unsubstituted amphetamines, rats showed a slight reduction in response rates with long pauses following reinforcement. After administration of the chloro-substituted compounds, the rat's response rate appeared irregularly depressed, and pauses between and after reinforcement became more frequent and were shorter than those with the unsubstituted amphetamines. The depression rate appeared more pronounced with the larger doses. The minimum effective doses of all compounds used ranged from 1 to 3.2 mg/kg. Except for the 1-(4-chlorophenyl)-2-aminopropane compounds, the *l* isomers of the chloro compounds appeared more potent (more active suppressants of FR behavior) than did the *dl* and *d* members.

Lilly Research Laboratories
Lilly and Company
Indianapolis, Indiana

- 1997 Owen, John E., Jr. **Psychopharmacological studies of some 1-(chlorophenyl)-2-aminopropanes. II. Effects on avoidance and discrimination behavior.** *Journal of Pharmaceutical Sciences*, 52(7):684-688, 1963.

Some 1-(chlorophenyl)-2-aminopropanes have been compared with *d*-amphetamine and methamphetamine for effects on avoidance and discrimination behavior in rats. Six male rats of the Long-Evans strain (300 to 450 g in weight) were trained to press a lever to avoid intermittent electroshocks. In alternate 10-minute periods, a rat received a time-out when no response on the lever was necessary. The doses of drugs studied were the two lowest that suppressed the appetite control behavior. After *d*-amphetamine (1.0 or 2.0 mg/kg), methamphetamine (1.0 or 2.0 mg/kg), and *dl* (2.0 or 3.2 mg/kg) and *d*-1-(4-chlorophenyl)-2-aminopropane (1.0 or 2.0 mg/kg), rats showed increased avoidance response rates, as well as responding during time-out periods, which was considered a loss of ability to discriminate. When given 3,4-dichlorophenyl or 2,4-dichlorophenyl-2-aminopropanes, the rats showed little or no change from normal in avoidance or discrimination behavior. These results indicate that, at the doses used, the chloro-substituted compounds produced less CNS stimulation than did *d*-amphetamine or methamphetamine.

(No address)

- 1998 Stretch, Roger. **Effects of amphetamine and pentobarbitone on exploratory behaviour in rats.** *Nature*, 199(4895):787-789, 1963.

The effects of a central depressant (pentobarbital) and a central stimulant (amphetamine) on exploratory behavior were studied in 70 black-hooded rats (35 male and 35 female) from 56 to 71 days of age. Observations of activity in a Y-maze were made 20 minutes after i.p. injections of pentobarbital (3.5, 7.0, and 10.5 mg/kg) and amphetamine sulphate (0.75, 1.5, and 2.25 mg/kg). Ten rats were randomly assigned to each drug level, and 10 controls received saline injections. Amphetamine reduced the activity of males and females, especially at the two higher dosages. Pentobarbital exerted no effect on the activity of males. The activity of the females increased at the two lower dosages and decreased at the third dosage. Females were more active than the males in both

drug treatments. Concepts of mechanisms of drug action with relation to exploratory behavior are presented.

Department of Psychology
The Queen's University of Belfast
Belfast, Ireland

1999 Koresko, Richard L., Snyder, Frederick, & Feinberg, Irwin. 'Dream time' in hallucinating and non-hallucinating schizophrenic patients. *Nature*, 199(4898): 1118-1119, 1963.

Seven hallucinating and four nonhallucinating patients were used to estimate the dream time in hallucinating and nonhallucinating schizophrenic subjects by studying EEG patterns and rapid eye movements (REM). The seven male and four female subjects ranged in age from 20 to 40 years. Four subjects were receiving either trifluoperazine, chloridazine, or procyclidine, alone or in combination, which was discontinued at least 7 days prior to recordings. Electrode attachments for recording vertical and horizontal REM and a unipolar left occipital EEG were led to an Offner type T electroencephalograph, which was run continuously at 15 mm/sec. Due to the difficulties in classifying EEG patterns, the following system was adopted for estimating time spent dreaming: each 20-second interval (one page of record) was scored for the presence of REM, spindles, and K-complexes. Dream time was taken as the number of pages on which a spindle or K-complex appeared in the absence of REM. The findings fail to support the hypothesis of a difference in dream time between hallucinating and nonhallucinating schizophrenic patients.

National Institute of Mental Health
National Institutes of Health
Bethesda, Maryland

2000 Carlton, Peter L. Behavioral stimulation due to alpha-methyl meta-tyrosine. *Nature*, 200(4906):586-587, 1963.

A study is made of behavioral stimulation in albino rats due to α -methyl-*m*-tyrosine (α -MT). Adult, male albino rats were trained on an operant, shock-avoidance schedule. The avoidance contingency was in effect for a period of 2 hours followed by a time-out

period of an hour. When avoidance and time-out performance had become reasonably stable, injections of saline (control) or α -MT (100 or 200 mg/kg i.p.) just before each session were begun. Control levels of responding were essentially constant over the six 2-hour avoidance periods, but α -MT produced a dose-dependent increase in responding. Increases in responding were maximal in 2 to 5 hours after injection of α -MT, with responding returning to normal in 8 to 10 hours. It is thought that the unexpected stimulation due to α -MT may be related to metabolic conversion of the drug to α -methyl-*m*-tyramine and, possibly, to β -hydroxy- α -methyl-*m*-tyramine in the brain.

Squibb Institute for Medical Research
New Brunswick, New Jersey

2001 Brittain, R. T., Lehrer, D. N., & Spencer, P. S. J. Phenylquinone writhing test: Interpretation of data. *Nature*, 200(4909):895-896, 1963.

In order to determine the value of the correlation between in vitro anti-5HT activity and the ability of a compound to antagonize phenylquinone-induced writhing, an investigation was made of the writhing response and its modification by compounds and procedures known to affect the activity and metabolism of biogenic amines. The compounds to be tested were given to six starved, male, albino mice (Tuck strain) 1 hour before an i.p. injection of phenylquinone, 2 mg/kg. Lysergic acid diethylamide (LSD) was found to be the greatest antagonist of both activities. Homochlorcyclizine, promethazine, and mepyramine, in descending order, were found to antagonize both activities. Phenylquinone (2 mg/kg), given to a group of mice daily for 5 successive days, caused a reduction in the number of writhes. Phenylquinone in a single injection was found to deplete 5HT. The sensitivity of adrenalectomized mice (5 days previously) to injected phenylquinone was increased (69% increase in writhes). The MAO inhibitors tranylcypromine (3.70 mg/kg), phenelzine (7.70 mg/kg), and iproniazid (112 mg/kg) given orally 4 hours before phenylquinone showed antagonistic activity to the writhing response. As a result of these tests, two additional classes of compounds, 5HT antagonists and MAO inhibitors, have been shown to be potent inhibitors of phenylquinone-induced writhing in mice.

Allen and Hanburys, Ltd.
Ware, Hertfordshire, England

2002 Megaugh, James L. & Petrinovich, Lewis. **Comments concerning the basis of learning enhancement with central nervous system stimulants.** Psychological Reports, 12:211-214, 1963.

In defending the viewpoint that CNS stimulants facilitate learning by potentiating the consolidation of the neural processes mediating learning, the opposing viewpoint, that CNS stimulants facilitate learning by reducing interfering stimulation (Thiessen et al., 1961), and the data from which it was derived are analyzed. Based on the analysis, the following conclusions are presented: (1) Many experimental observations cannot be explained by the reduction of interference theory. (2) The experimental data of Thiessen et al., are irrelevant to the question of the relationship between posttrial locomotor activity and learning, and also allow little generalization concerning the effect of strychnine on locomotor (or exploratory) behavior.

University of Oregon
Portland, Oregon

2003 Rumelhart, David E. & Mueller, Marvin R. **Enhancement of amphetamine sulphate effects by atropine in a social situation.** Psychological Reports, 12:251-254, 1963.

In order to determine whether the enhancement of amphetamine effects by atropine would occur in a situation termed an "approach" as contrasted to an "avoidance" situation, 40 adult albino rats (150 days of age) were divided into four groups of 10 each. One group received two successive injections of saline i.p.; the second group received a saline injection followed by 5.0 mg/kg of atropine sulfate; the third group received saline followed by 1.0 mg/kg of amphetamine sulfate; and the fourth group received 5.0 mg/kg of atropine and 1.0 mg/kg of amphetamine. In addition to these rats, another group was used as stimulus animals and was placed, three at a time, in a box divided by a barrier. The experimental rats were placed singly on the opposite side of the barrier. The frequencies of five behaviors were analyzed; these included locomotion, sniffing, grooming, inactivity, and barrier-directed behavior. The latter behavior was considered to be the pertinent dependent variable in this

study. Five-minute observations were made at 30, 60, and 90 minutes after injection. The atropine-amphetamine group spent significantly more time in barrier-directed behavior than did the rats in the saline-saline and saline-atropine groups during all three observations' sessions and significantly more time than did the saline-amphetamine group during the observations made at 60- and 90-minutes.

State University of South Dakota
Vermillion, South Dakota

2004 Thompson, William R., Goldenberg, I., Watson, J., & Watson, M. **Behavioral effects of maternal adrenalin injection during pregnancy in rat offspring.** Psychological Reports, 12:279-284, 1963.

This report describes the possible relationship between two stress parameters (intensity and trimester administration of adrenalin) and behavioral effects in rat offspring. Sixty female and 60 male, Sherman albino rats were divided into 12 matched control (3 groups) and experimental groups (9 groups). Of the 400 offspring born from the 60 matings, 240 were used for behavioral testing. The experimental treatment consisted of high (3 cc of 1:1,000 solution adrenalin chloride/kg body weight) or low (cc of 1:1,000 solution adrenalin chloride/kg body weight) dosages of adrenalin chloride or saline during one of three trimesters of pregnancy. The three control groups received no injection of any kind. In the open field test (normal and stress condition), males from mothers injected in the second trimester showed a depression in activity level. The same trimester dosage interaction showed up less strongly in the female offspring. Performance in the runway test, in the water-maze apparatus, and error scores in the Hebb-Williams maze were not affected by the experimental treatment. In general, these experiments reported were successful in demonstrating some behavioral effects in offspring as a result of prenatal maternal stress, but did not afford a specification of those parameters responsible for the particular kind, magnitude, and direction of effects observed.

Wesleyan University
Middletown, Connecticut

- 2005 Cole, Sherwood O. **Interaction of amphetamine with conditions of food deprivation.** Psychological Reports, 13:387-390, 1963.

This study was designed to test the hypothesis that there is an interaction between amphetamine and conditions of food deprivation. Twenty-four 140-day-old female hooded rats (200 to 300 g body weight) were randomly assigned to one of two *d*-amphetamine sulfate dosage levels (5 mg/kg or 10 mg/kg i.m.) and one of three food deprivation conditions (0, 12, or 24 hours). The amount of food consumed during a 3-hour feeding period was determined for four separate trials. On each trial, the 3-hour feeding period was preceded by a single injection of amphetamine and a single condition of food deprivation. The mean amount of food consumed by subjects in the 5 mg/kg, 12-hour deprivation group and that consumed by subjects in the 5 mg/kg, 24-hour deprivation group was greater than that consumed by subjects in either of the other experimental conditions. A considerable amount of hyperactivity was observed among subjects receiving 10 mg/kg dosage, but little hyperactivity was observed for those receiving 5 mg/kg.

Claremont Graduate School
Claremont, California

- 2006 Ross, Sherman & Schnitzer, S. B. **Further support for a placebo effect in the rat.** Psychological Reports, 13:461-462, 1963.

In order to add supporting data to the reported apparent placebo effect of prior administration of a drug, 30 male hooded rats (107 to 134 days of age) were used. Ten rats each were assigned to the following experimental groups: DR (Drug-Run), 0.85 to 1.20 cc of *d*-amphetamine i.p.; DNR (Drug-Not Run), 0.74 to 1.20 cc of the same drug in an isotonic solution; and the UR (Untreated-Run). The UR group had a needle inserted i.p. prior to testing. Both the DR and DNR groups received 3.0 mg/kg i.p. of *d*-amphetamine in the first week of testing. Activity measurements demonstrated significantly more locomotion in the DR group than in the UR group. There was no significant difference statistically in the amount of activity in the second week's testing of the DNR group and that in the first week's test of the UR rats. The results confirm the findings reported

earlier that a single administration of a drug may have consequences for later behavior, over and above any direct actions of the drug.

American Psychological Association
Central Office
Washington, D. C.

- 2007 Griffiths, William J., Jr. **Effect of hydroxylamine on audiogenic seizures in the laboratory rat.** Psychological Reports, 13:755-759, 1963.

The effect of i.p. injection of hydroxylamine on the susceptibility of rats to audiogenic seizures was studied in 31 adult inbred male Wistar rats (60 days old). The normal incidence of audiogenic seizure was determined in six predrug trials. Seizure susceptibility was tested again at 5 minutes, 1, 5, 15, and 25 hours following i.p. injection of 0.1 cc/100 g hydroxylamine. One week later, the animals were retested for seizure susceptibility. Hydroxylamine showed a significant effect on the seizure pattern in some animals, but its action was variable and highly individualized. Hydroxylamine is known to raise brain GABA levels. It was concluded that the etiology of audiogenic seizures cannot be directly related to increased GABA levels.

Montana State University
Missoula, Montana

- 2008 Heckel, R. V., Wiggins, S. L., & Crasson, J. K. **Effects of methandrostenolone (dianabol) on old male rats.** Psychological Reports, 12:651-654, 1963.

The effects of methandrostenolone were studied in two experiments in old, male rats, with regard to activity level, reactivity to both male and female rats, and body weight. Ten male, albino, Charles River C-D strain rats over 2 years of age were used in both experiments. In the first experiment, bar-pressing behavior for food reinforcement was determined. Five control rats received 0.1 cc of saline s.c., and five experimental rats received 9.1 cc of the drug s.c. In the second

experiment, the Peacock--Williams ultrasonic device was used to measure activity of the rats in living cages. Rats were placed in an empty cage, then each rat was exposed first to a male rat and then to a female rat, and changes in activity were noted. Methandrostenolone increased the activity level in the bar-pressing experiments and in the presence of females. Body weight increased, even under the increased activity level, and coat color improved.

Veterans Administration Hospital
Augusta, Georgia

- 2009 DiMascio, Albert. Drug effects on competitive-paired associate learning: Relationship to and implications for the Taylor manifest anxiety scale. *Journal of Psychology*, 56(1):89-97, 1963.

The relationship between the anxiety-reducing and hypnotic properties of psychotropic drugs (phenyltoloxamine, secobarbital, and meprobamate) and performance on a competitive-paired-associate list (CPAL) of words was studied in 16 physically and mentally healthy, male college students. Each student participated in four experiments carried out at 1-week intervals. All students were interviewed by a psychiatrist and given the Taylor Manifest Anxiety Scale (TMAS) prior to the experiments. They were divided into two groups of 8 subjects each, one group receiving a single dose of 100 mg phenyltoloxamine, 200 mg meprobamate, 100 mg secobarbital, and a placebo, and the other group receiving 200 mg phenyltoloxamine, 400 mg meprobamate, 50 mg secobarbital, and a placebo. The drugs were administered under a double-blind procedure. The CPAL task consisted of 16 pairs of words (stimulus words and response words). The CPAL performances under the various drug conditions were examined as they related to the predrug TMAS scores and to the drug-induced changes in anxiety and sleepiness. Individuals with higher TMAS scores who took 800 mg meprobamate made fewer errors and took fewer trials to learn the CPAL lists than did those with lower TMAS scores. There was a similar relationship between TMAS scores and error measurement after 50 mg secobarbital and 200 mg phenyltoloxamine. None of the drugs produced consistent or marked alterations in self-ratings of anxiety, but individual variations were noted. The subjects reporting the greatest degree of sleepiness after 800 mg meprobamate learned the lists in fewer trials and with

fewer errors than did those who were unaffected or were not sleepy. At 40 mg secobarbital and 400 mg meprobamate, the same relationship approached statistical significance for the trials. The TMAS scores were not related to CPAL performance under the placebo. The greatest degree of hypnosis was after 200 mg phenyltoloxamine and 100 mg secobarbital.

Massachusetts Mental Health Center
Psychopharmacology Research Laboratory
74 Fenwood Road
Boston 15, Massachusetts

- 2010 Wagner, Allan R. Sodium amytal and partially reinforced runway performance. *Journal of Experimental Psychology* 65(5):474-477, 1963.

Acquisition performance of rats in a simple runway was investigated as a function of the percentage of reinforced trials (100% versus 50%) and the effect of sodium amytal or saline in a 2 x 2 fractional design. Forty-eight male, albino Sprague--Dawley rats were divided into four groups. Two groups received 20 mg/kg sodium amytal and two received equal volumes of isotonic saline. Within each injection condition, one group received 100% reinforcement and one group received 50% reinforcement. In the saline-treated groups, 50% reinforcement induced faster final speeds on the runway than did 100% reinforcement. In the amytal-treated group, the reverse was true. The results were predicted from a frustration theory interpretation of random partial reinforcement and from the assumption that anticipatory frustration is particularly susceptible to the depressant action of sodium amytal.

Yale University
New Haven, Connecticut

- 2011 Ende, Robert N. The use of intravenous sodium amytal to overcome resistance to hypnotic suggestion. *American Journal of Clinical Hypnosis*, 6(2):169-171, 1963.

A case history of a 30-year-old man is presented, which describes the use of hypnosis and sodium amytal in the treatment of aphonia. On a previous admission, sodium amytal had been used alone to relieve the aphonia.

but treatment was not successful. The patient resisted hypnotic suggestion on three interviews; on the fourth, after hypnosis was induced, a slow infusion of sodium amytal was administered. When 350 mg of the drug had been infused, the patient began speaking. He was, thereafter, able to speak while under hypnosis without the aid of medication. This technique is useful in cases in which immediate treatment is needed, but in which resistance to hypnotic suggestion is encountered.

University of Colorado
Denver 20, Colorado

- 2012 Hughes, Francis W. & Forney, Robert B. **Delayed audiofeedback (DAF) for induction of anxiety: Effect of nortriptyline, ethanol, or nortriptyline-ethanol combinations on performance with DAF.** *Journal of the American Medical Association*, 185(7):556-558, 1963.

In order to quantitate performance in normal subjects under an anxiety induced situation, and to study the effect of ethanol and nortriptyline on performance, an experiment was made using 16 normal subjects from 20 to 39 years of age with a median weight of about 155 pounds. Delayed audiofeedback induced anxiety in the performance of tests on verbalization, mathematics, and color differentiation. The 16 subjects were divided into two groups with 8 receiving a total of 40 mg nortriptyline (four 10-mg capsules) and 8 receiving 100 mg (four 25-mg capsules) of the drug. The alcoholic beverage was 3 oz of 100-proof whiskey. Treatment schedules were alcoholic beverage plus nortriptyline, alcoholic beverage plus placebo, placebo beverage plus nortriptyline, and placebo beverage plus placebo. Blood alcohol level was 50 mg/100 cc. There was a decrease in performance after ethanol ingestion. Neither drug dose appeared to antagonize or potentiate the action of ethanol. There was no difference in performance at the two dose levels of nortriptyline, with the exception of one test at the 25-mg level.

Indiana University
Bloomington, Indiana

- 2013 Youniss, James & Furth, Hans G. **Reaction to a placebo: The mediational deficiency hypothesis.** *Psychological Bulletin*, 60(5):499-502, 1963.

Data previously interpreted by an investigator as supporting the hypothesis that

verbal mediation is a function of age level are reexamined. In comparing this interpretation with the data presented by other investigators whose experimental work has dealt directly with the relationship of language to development, it is concluded that the mediational deficiency hypothesis is an oversimplification of a complex issue, whose solution has been shown to be resistant to simple explanations.

Catholic University of America
Washington, D.C.

- 2014 Tengesdal, M. **Experiences with intracarotid injections of sodium amytal. A preliminary report.** *Acta Neurologica Scandinavica*, 39:329-343, 1963.

The use of intracarotid injection of sodium amytal as a diagnostic tool in 34 patients with different supratentorial lesions, including epilepsy, arteriovenous aneurysms, atrophies, and tumors, is discussed. A 5% solution of sodium amytal was given in either side in doses varying between 25 to 100 mg with a 30 to 40 minute interval between injections. Injections of less than 20 mg amytal did not produce any changes in the EEG. With doses of 20 to 25 mg, low-voltage fast activity was apparent on the side of injection. Larger amounts of amytal produced ipsilateral slowing. The slowing increased proportionally to the amount of amytal injected. Sodium amytal usually produced characteristic changes in the EEG and reversible neurological deficits, which were predominantly from the ipsilateral hemisphere and consisted of a variety of symptoms. Sopor, semicoma, coma, homonymous hemianopsia, deviation of the bulbi, different degrees of sensory and motor deficits, aphasia, and dysarthria were some of the symptoms noted; there were changes in reflexes also. Injections on the right side usually produced anosognosia. Clinical deficits were transient and usually detectable only during the first 3 minutes after injection. Ipsilateral injections suppressed unilateral cortical epileptogenic foci but contralateral injection had no such effect. In a patient with a small arteriovenous aneurysm and cases of localized cerebral atrophy, response to amytal was much more pronounced on the side of the aneurysm or atrophy. In the cases of cerebral tumors, there was an asymmetric response to intracarotid injections of the drug, and the reaction depended upon the localization and size of the tumor.

University of Oslo Hospitals
Oslo, Norway

- 2015 Reynolds, Herbert H., Rohles, Frederick H., Jr., Fineg, Jerry, Back, Kenneth C., & Thomas, Anthony A. **The effect of UDMH on learned behavior in the Java monkey.** *Aerospace Medicine*, 34:920-922, 1963.

To determine the psychological effects of 1,1-dimethylhydrazine (UDMH), the performance of a response--shock avoidance task by four male Java monkeys (about 3 years of age) was studied. Electric shock and photo stimuli were used in the conditioning. Two control animals were injected i.p. with saline and two experimental animals received 30 mg/kg i.p. UDMH. The same task schedule was used in the drug phase as was used in the predrug experiment. UDMH content in the blood was also measured. The statistical analysis yielded a t-ratio of 8.39 between the control and experimental groups. When each was considered his own control, the t-ratios from the two experimental animals were both significant beyond the 0.01 level, while the ratios for the two controls were not significant. A second experiment was done to test the reliability of the findings using the same methods as in the first experiment except that no blood samples were taken. The t-ratio between the control and experimental groups was not significant, nor was it significant when each animal was considered his control. A third experiment was done because of the contradictory results of the first and second experiments. The methods were still the same, but seven subjects were used (four experimentals and three controls). Again the statistical results were not significant. Only one experimental animal showed a significant decrement in performance. The conclusion is made that 30 mg/kg UDMH is insufficient to produce significant changes in simple learned behavior.

6571st Aeromedical Research Laboratory
Holloman Air Force Base, New Mexico

- 2016 Vojtechovský, M., Horácková, E., & Kuhn, E. **Vliv jednorázového podání thymoleptik cs. výroby na psychiku zdravého člověka. (The effect of single administration of some Czechoslovak thymoleptics on the psychic function in healthy man.)** *Activitas Nervosa Superior*, 5:173-175, 1963.

A group of 15 healthy, paid volunteers, average age 30 years, was given in a double-blind fashion 50 mg of the antidepressants

amitriptyline, chloramitriptyline, proheptatriene, prothiadene, propazepine, and imipramine p.o. Placebo and pentobarbital (0.1 g) served as the control dosage. The subjects were given physiological and psychological tests, beginning 2 or 3 hours after the drug; these tests included: pulse rate, blood pressure, blinking rate, EEG, ataximetry, arithmetic subtraction, differentiation of syntactically presented text, estimation of time, and the color test of Luscherov. During the 6- to 8-hour test sessions, the subjects completed mood and vegetative questionnaires every hour and a modified emotionality questionnaire every 2 hours. Vegetative reactions were produced by the drugs in the following decreasing order: proheptatriene, chloramitriptyline, pentobarbital, amitriptyline, imipramine, prothiadene, propazepine, and placebo. Placebo produced no reaction in one-third of the subjects, produced vegetative disorder in one-third, and had psychostimulative effect in one-third. None of the drugs improved conceptualization, and in the cases of proheptatriene and chloramitriptyline, efficiency decreased and errors increased. Projection was potentiated only by pentobarbital and proheptatriene. In some subjects, psychostimulative effect was produced only by propazepine and prothiadene. The various effects of each drug on the total behavior of the subjects are described.

Institute for Research on Human Nutrition
Prague, Czechoslovakia

- 2017 Doty, Barbara A. & Doty, Larry A. **Chlorpromazine-produced response decrements resulting from chronic administration in infancy.** *Canadian Journal of Psychology*, 17(1):45-51, 1963.

A study was made to ascertain the effects chronic administration of chlorpromazine (2 mg/kg i.p.) for 53 days (beginning with 3-day-old rats) on subsequent learning and extinction of a complex response and on the persistence of such learning after drug discontinuation. Controls received saline injections. Forty hooded rats, equally divided between the sexes, were exposed to both a conditioned and an unconditioned stimulus. Mean body weights were obtained at 3-day intervals to determine if the drug affected general physical development. Avoidance, effective escape, and failure to respond were scored during each trial. Extinction trials were begun 5 days after

the last acquisition trial. A relearning trial series (60 and 120 days after learning) was done to determine the persistence of the effects of drug treatment. The chlorpromazine-treated rats made significantly fewer successful avoidance responses than did the controls, and the mean number of effective escapes was also reduced. Response failures during extinction were facilitated by the drug. There was a persistence of response decrements in experimental animals for as long as 120 days after the termination of drug treatment, which suggests a serious interference with later adaptive problem-solving behavior.

North Central College
Naperville, Illinois

2018 Ross, W. D., Adsett, Nancy, Gleser, Goldine, Joyce, C. R. B., Kaplan, S. M., & Tieger, M. E. A trial of psychopharmacologic measurement with projective techniques. *Journal of Projective Techniques*, 27(2):222-225, 1963.

Forty hypotheses and nine qualifying subhypotheses were used to predict the differential effect on projective test scores of 80 medical students who had been given orally, in a double-blind arrangement, either 10 mg dextroamphetamine, 65 mg amobarbital, or a lactose placebo. The projective tests used were a word association test, the Rorschach method, the Rosenzweig frustration tolerance test, and a 5-minute written sample based on the verbal sampling technique. The treatment-administration design permitted both cross sectional and matched comparison of drug effects. Although only 20% of the hypotheses and 33-1/3% of the qualifying subhypotheses received confirmation at the required level of probability, there was only one instance of a significant finding contrary to a hypothesis. There was no overall difference in predictability in relation to the two drugs. The predictions for the Rorschach scores were somewhat better supported than were those for the other projective techniques.

University of Cincinnati
Cincinnati, Ohio

2019 Fazio, C., Giberti, F., Rossi, R., & De Carolis, V. Pharmacodynamic reactivity in mental patients measured by fractionated "Weckanalyse". *Comprehensive Psychiatry*, 4(4):246-255, 1963.

In order to determine whether changes induced by methylamphetamine and methylphenidate were significant in discriminating

among some clinical states and psychopathological syndromes, psychopathological responses (psychic threshold) and vegetative behavior (pulse rate and blood pressure) were used as parameters in determining the "stimulation threshold." The patients were administered 30 mg i.v. of methylamphetamine or methylphenidate at the rate of 1 mg every 30 seconds. Both drugs were administered by the same experimenters and in the same environmental conditions. Twenty-four hours before the drug was tested, 30 cc of a single saline solution was administered i.v. It was observed that the threshold value varies in relation to the psychiatric diagnosis. The mean threshold values varied in increasing order from neurotics, to atypically depressed, to schizophrenics, to endogenously depressed patients. The mean threshold appeared to be much higher in those patients who had responded to ECT than in those who had responded favorably to drugs. No statistical significance was found in the threshold values after methylphenidate in discriminating the psychotics from the neurotics. The maximum percent change (M.P.C.) of the pulse rate or the blood pressure after methylphenidate seems to differentiate the schizophrenics from the neurotics or depressives, and the M.P.C. is more elevated in the patients cured or improved by ECT than by drug therapy.

University of Genoa
Genoa, Italy

2020 Sheth, U. K., Vaz, A., Deliwala, C. V., & Bellare, R. A. Behavioural and pharmacological studies of a tranquilising fraction from the oil of *Celastrus paniculatus* (Malkanguni oil). *Archives Internationales de Pharmacodynamie et de Therapie*, 144(1-2):34-50, 1963.

Behavior and other pharmacological effects of an active principle isolated from the oil of *Celastrus paniculatus* (Malkanguni oil), designated as fraction Mal-III/A, are reported. Fraction Mal-III/A produced tranquilization in cats, monkeys, mice, and rats at 200 mg/kg i.p. This fraction at 200 mg/kg also potentiated the effect of sodium hexobarbital (100 mg/kg) and produced hypothermia in mice. In small doses (100 or 200 mg/kg i.p.), Mal-III/A protected rats against metrazol (70 mg/kg s.c.), and decreased mortality due to amphetamine (14 mg/kg s.c.) in grouped mice at a dose of 100 mg/kg, but on increasing the dose of Mal-III/A to 200

or 500 mg/kg, the protection decreased. Spontaneous motor activity, amphetamine-induced hyperactivity, orientation hyperactivity, and oxygen consumption in mice were decreased by Mal-III/A at 200 or 500 mg/kg. Diminution of carotid occlusion reflex and hypotension occurred with fraction Mal-III/A at 20 mg/kg i.v. At a dosage of fractions 200 mg/kg, Mal-III/A and Mal-III/B produced salivation, vomiting, defecation, and tremors in cats and dogs.

G.S. Medical College
Bombay 12, India

- 2021 Hughes, Francis W., Rountree, Clyde B., & Forney, Robert B. **Suppression of learned avoidance and discriminative responses in the rat by chlordiazepoxide (Librium) and ethanol-chlordiazepoxide combinations.** *Journal of Genetic Psychology*, 103: 139-145, 1963.

The effects of chlordiazepoxide and chlordiazepoxide-alcohol combinations on learned avoidance and discriminative responses in the rat were investigated. A modified shock-avoidance box was used to train male, albino weanling rats of the Wistar strain (55 g body weight). All rats were trained to escape the impending shock correctly, and were then given ethanol (0.5 mg/kg i.p.), chlordiazepoxide (10, 20, or 30 mg/kg i.p.), or a mixture of the two drugs i.p. Chlordiazepoxide (20 or 30 mg/kg) produced suppression of learned avoidance responses with little change in discriminative responses. Alcohol caused a reduction in avoidance responsiveness only when a decrease in discrimination resulted. A reversal of the avoidance reducing property of chlordiazepoxide was caused by the administration of alcohol to rats treated with the chlordiazepoxide-ethanol mixture. This inhibition lasted longer than the period in which alcohol could be detected in the blood. Resulting data indicate that chlordiazepoxide has properties that classify it as a tranquilizer. Alcohol demonstrates properties that are more typical of non-ataractic depressants, such as the barbiturates.

Indiana University School of Medicine
Indianapolis, Indiana

- 2022 Haywood, Carl H. & Hunt, J. McV. **Effects of epinephrine upon novelty preference and arousal.** *Journal of Abnormal and Social Psychology*, 67(3):206-213, 1963.

A test of novelty preference was administered to human subjects before and after injections of epinephrine and of sterile Ringer's solution in order to obtain evidence relevant to a choice between a theoretical interpretation asserting that it is an optimum of arousal that determines whether a person will approach or withdraw from a source of novel input, and another interpretation asserting that it is an optimum of incongruity that is crucial. The subjects, 45 civil service employees (5 psychologists, 6 nurses, 31 nursing assistants, and 3 secretaries) were assigned to one of three experimental conditions---injections of 0.8 mg of epinephrine, 0.4 mg of epinephrine, or Ringer's solution. The scores for novelty preference were no more altered by epinephrine than by Ringer's solution. Epinephrine did not increase palmar sweating, which has been found to be associated with encountering incongruity, but it did increase arousal, as indicated by increased heart rate and pulse pressure. The failure of epinephrine to affect novelty preference has diminished relevance to the issue of whether the optimum determining direction of response to incongruous input is one of arousal or of incongruity.

George Peabody College
Nashville, Tennessee

- 2023 Randrup, A., Munkvad, I., & Udsen, **Adrenergic mechanisms and amphetamine induced abnormal behaviour.** *Acta Pharmacologica et Toxicologica*, 20(2):145-157, 1963.

Amphetamine-induced abnormal behavior was observed in rats, and the effects of various α - and β -adrenergic blocking agents and tranquilizers on this abnormal behavior were studied. White male rats (3 to 6 months old, 160 to 350 g in weight) were given doses of 1.5 or 3.0 mg/kg d -amphetamine. The tryptamine analog of amphetamine, α -methyltryptamine, was also given to rats in doses of 80, 40, 20, and 10 mg/kg to determine whether a behavioral response similar to the amphetamine-induced response could be elicited. The following drugs were studied:

for effect on the behavior pattern: (1) α -adrenergic blocking agents---phenoxybenzamine, dihydroergotamine, Hydergine (a combination of dihydroergocornine, dihydroergocristine, and dihydroergokryptine), and phentolamine; (2) β -adrenergic blocking agents---nethalide and dichloroisopropyl-noradrenaline; and (3) tranquilizers---reserpine, chlorpromazine, haloperidol, and ethoxybutamoxane. Two patterns of abnormal behavior are described, one elicited at a dose of 1.5 mg amphetamine and the other at 3.0 mg amphetamine. None of the α - and β -adrenergic blocking agents showed any effect on the behavioral pattern elicited by 3 mg/kg amphetamine. Reserpine caused no inhibition of the behavioral pattern, but haloperidol (0.12 mg/kg), chlorpromazine (12 mg/kg), and ethoxybutamoxane (3 mg/kg) were effective antagonists. The α -methyltryptamine (40 mg/kg) elicited the same behavioral pattern as 3 mg/kg amphetamine. The specificity of the receptors involved in the behavioral effects of amphetamine and α -methyltryptamine is discussed.

St. Hans Hospital
Roskilde, Denmark

- 2024 Ruffin, J. B. **Functional testing for behavioral toxicity: A missing dimension in experimental environmental toxicology.** *Journal of Occupational Medicine*, 5:117-121, 1963.

The functional testing for behavioral toxicity of industrial chemicals as it now exists has been criticized, and new approaches have been suggested. The techniques employed by foreign investigators and also the type of study conducted in the U. S. are discussed. In conclusion, the author states that worthwhile work in determining the complex behavioral effects of drugs cannot be accomplished by the toxicologist without the active participation of a well-trained experimental psychologist.

University of Oklahoma Medical Center
Oklahoma City, Oklahoma

- 2025 Heuschele, Werner P. **Chlordiazepoxide for calming zoo animals.** *Journal of the American Veterinary Medical Association*, 139:996-998, 1962.

The effects of chlordiazepoxide in 22 animals of 18 genera in a zoo environment are discussed. The drug was administered

orally, intravenously, or intramuscularly according to body weight. The latter two routes were used in the larger or more aggressive animals. Polysorbate 80 was the diluent. The drug was found effective in tranquilizing newly admitted species, who were frightened, and in taming aggressive animals. The four negative responses were found in the Sumatran tiger, the Hensel's cat, the tapir, and the klipspringer. There was no evidence of toxicity at the dose levels used.

San Diego Zoological Gardens
San Diego, California

- 2026 Nowlis, Vincent. **Methods for studying mood changes produced by drugs.** *Revue de Psychologie Appliquée*, 11:373-386, 1961.

A general discussion is presented of the various meanings of mood, interpretations of mood changes, and possible methods of measuring mood terms. In studying drug effects, the use of mood terms is frequently necessary. Three stages in the critical reformation of a popular term, such as "mood," are defined and discussed. In a revised definition of mood, it is suggested that mood is the effect on the self of its own configurations of activity, and that awareness is a concomitant of that effect and, thus, a concomitant mood. Methods of studying mood in relation to self, configurations of activity, and awareness are presented. The behavior and experience of a subject are dependent, in part, on the social situation, on the current psychophysiological status and current expectancies of the subject, and on the complex social interactions that are developed during the course of an experiment.

The University of Rochester
Rochester, New York

- 2027 Boissier, Jacques R. & Simon, Pierre. **La réaction d'exploration chez la souris. (Exploratory reaction in mice).** *Thérapie*, 17:1225-1232, 1962.

A test for psycholeptic drugs, based on the exploratory reaction of mice in a new environment, is described. Mice were placed

individually in an enclosure, which had on the floor 16 regularly placed holes. The number of times the mouse placed his head in a hole was observed, and the number of holes explored was determined after 1, 2, 3, 4, and 5 minutes. The mean was calculated for each minute and for the 5-minute total. Chlorpromazine (0.25 to 1.5 mg/kg) and procalmadiol (25 to 150 mg/kg) were administered i.p., and observations of treated mice were compared with those of the controls. Both drugs, even in small doses, reduced the number of holes explored, and it was concluded that the test described is a valid entry into the battery of tests already used to observe the effects of psycholeptic drugs.

15 rue de l'Ecole de Médecine
Paris, France

See also: 1906, 1907, 1914, 1922, 1957,
2028, 2064

PHARMACOLOGY

- 2028 van Orden, Lucas S. & Sutin, Jerome.
Differential effects of norepinephrine on responses evoked in the hypothalamic ventromedial nucleus. Electroencephalography and Clinical Neurophysiology, 15:796-803, 1963.

The action of local or intracarotid injection of norepinephrine upon responses evoked in the hypothalamic ventromedial nucleus (HVM) of adult cats is the subject of this report. Twenty-nine adult cats, anesthetized with sodium pentobarbital (40 mg/kg), were injected i.a. through one or both carotid arteries or locally through a bipolar electrode with a stylet. The injection of 20 μ g to 55 μ g norepinephrine (crystalline or liquid) directly into the HVM or identical concentrations of norepinephrine (liquid) into the ipsilateral carotid artery increased the amplitude of the HVM response to septal stimulation and suppressed the HVM response to amygdaloid stimulation. Comparable concentrations of epinephrine produced similar results, whereas *d*-amphetamine produced a suppression of both septal-HVM and amygdaloid-HVM responses. Local injections of 0.85% saline, pitressin, or sodium nitrite did not alter the HVM evoked responses. The changes following norepinephrine injections were probably due to the drug's action upon 2 separate populations of cells that are spatially overlapping. The site of action of drugs injected into the carotid artery may be widespread, whereas local injections should have a restricted locus of action.

Yale University School of Medicine
 New Haven, Connecticut

- 2029 Cahn, Burton, Brahen, Leonard S., Wiseman, Edward H., & Pinson, Rex, Jr. **Urinary excretion of benzquinamide in humans.** Current Therapeutic Research, (6):301-304, 1963.

The urinary excretion of benzquinamide was measured following drug administration p.o., i.m., and by rectal suppository. Four normal male prisoners were used in the study. Over a 3-week period, each volunteer received one form of the drug on a planned

dosage schedule every third day. On the first day, all subjects received 100 mg p.o.; on the fourth day, 100 mg i.m.; and on the seventh day, 100 mg by rectal suppository. During the second round of 3-day intervals, dosage was increased to 200 mg, and on the third round it was increased to 300 mg. Excretion patterns indicate that benzquinamide is rapidly and completely absorbed after p.o. administration and slowly and incompletely absorbed when given as a rectal suppository. Total urinary excretion as unchanged benzquinamide was 3% to 7% following p.o. administration, 3% to 15% following i.m. administration, and 0% to 3% when given as a suppository. The greater excretion following i.m. administration is presumably because the drug reaches the kidneys without traversing the liver.

1930 Chestnut Street
 Philadelphia, Pennsylvania

- 2030 Gey, K. F., Burkard, W. P., & Pletscher, A. **Influence of chlorpromazine on decarboxylases of aromatic amino acids.** Biochemical Pharmacology, 8:383-387, 1961.

The influence of chlorpromazine on decarboxylation of 5HTP and DOPA was investigated in vitro and in vivo in the brain and kidney of rats. Pools of brains (excluding the medulla oblongata) and of decapsulated kidneys were homogenized in 3 or 4 ml per g organ of ice-cold phosphate buffer. Chlorpromazine 10^{-3} M and 10^{-4} M added to DOPA and 5HTP substrates, with and without the addition of pyridoxal-5'-phosphate (py-5-p), showed that 10^{-4} M concentration did not influence decarboxylation of 5HTP or DOPA in the brain and kidney. The 10^{-3} M chlorpromazine only inhibits DOPA decarboxylation in the brain supernatant in the absence of py-5-p. In rats pretreated with 20 to 75 mg/kg/i.p. chlorpromazine, no significant effect on decarboxylation of 5HTP or DOPA in the brain, whether or not py-5-p was added to the medium, was demonstrated. There was a significant increase in decarboxylation of both amino acids in the kidney provided that no py-5-p was added to the medium. The

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results are discussed with regard to the effects of chlorpromazine on the metabolism of py-5-p and aromatic monoamines.

Medical Research Department
F. Hoffmann-La Roche & Co. Ltd.
Basel, Switzerland

- 2031 Back, Kenneth C., Pinkerton, Mildred K., & Thomas, Anthony A.
Therapy of acute UDMH intoxication. *Aerospace Medicine*, 34(11):1001-1004, 1963.

This report concerns both symptomatic and antidotal treatment by acute 1,1-dimethylhydrazine (UDMH) intoxication and especially the effects of 2 Vitamin B₆ congeners, pyridoxine hydrochloride (PIN-HCl) and pyridoxamine dihydrochloride (PAM-2HCl). Pentobarbital, methitural, phenobarbital, amobarbital, and diphenylhydantoin all failed to control seizures or prevent death in 7 dogs given 100 mg/kg i.v. or i.p. of UDMH. The effective doses of PIN-HCl and PAM-2HCl were determined in several different species and are as follows: mice, ED₅₀ = 38 mg/kg PIN-HCl and 62 mg/kg PAM-2HCl; rats, ED₅₀ = 100 mg/kg PIN-HCl and 10 mg/kg PAM-2HCl; dogs, ED₅₀ = 150 mg/kg PIN-HCl; and monkeys, ED₅₀ = 50 mg/kg PIN-HCl and 150 mg/kg PAM-2HCl. Vomiting in dogs and monkeys was the only manifestation that was not abolished by this therapy. The species difference in the protective efficacy of PIN-HCl and PAM-2HCl is probably caused by species differences in the metabolism of B₆ analogs. It is concluded that for human treatment of UDMH toxicity, PIN-HCl should be used.

Aerospace Medical Division
Wright-Patterson Air Force Base
Dayton, Ohio

- 2032 Kobayashi, Tsukasa & Himwich, Harold E. **Effects of trifluoperazine on rabbit EEG.** *Journal of Neuro-psychiatry*, 5(2):123-131, 1963.

An EEG analysis was made of the possible sites of action of chronic and acute administration of trifluoperazine on the rabbit brain. Forty-seven New Zealand albino rabbits (weight, 1.9 to 4.7 kg), of which 26 were used for acute medication and 21 for chronic medication, were tracheotomized and maintained by artificial respiration. Coaxial electrodes were used for recording the electrical activity of the brain, and blood pressure was observed by means of a cannula inserted in a femoral

artery and connected to a mercury manometer. The acute i.v. administration of the drug produced high-voltage slow activity and blocked arousal responses in small dosages (below 6 mg/kg), whereas higher dosages (above 6 mg/kg) exhibited continuous alert patterns. Chronic injection of small dosages (2 mg/kg i.p. or i.m.) produced an arousal pattern in the EEG when chronic medication facilitated abnormal seizure discharges from the hippocampus or amygdaloid nuclei and produced a state of high excitability of these sites, rendering these structures sensitive to the stimulation.

University of Tokyo
Bunkyo-ku
Tokyo, Japan

- 2033 Trzebski, Andrzej. **Badania nad osrodkowym dzialaniem neurohormonow. II. Dzialanie serotoniny i rezerpiny na osrodki sercowo-naczyniowe podwzgorka i tworzenia siatkowatego pnia mozgu.** (Studies on the central action of neurohormones. II. Action of serotonin and reserpine on cardiovascular centers of the hypothalamus and reticular formation.) *Acta Physiologica Polonica*, 8(1):77-91, 1962.

Serotonin, introduced into the hypothalamus and various points of the reticular formation, diminished the amplitude of action potentials and the excitability of both pressor and depressor points. Microinjections of serotonin into the tegmentum of the midbrain caused transient hypotensive effects. Injected into the third ventricle the drug diminished the excitability of pressor and depressor cardiovascular centers of the hypothalamus and brain stem. Given similarly in doses of 0.1 mg, it occasionally intensified the effects of stimulation of inhibitory structures. Atropine i.v. did not suppress the hypotensive effects. The MAO inhibitors, iproniazid and harmaline injected into the third ventricle prior to serotonin reversed its hypotensive effect. Epinephrine and norepinephrine in microinjections into brain tissue or into the third ventricle suppressed the inhibitory effect of serotonin on both the action potential amplitude of the reticular formation and excitability of cardiovascular pressor centers. Reserpine, injected into the third ventricle, usually did not affect arterial blood pressure. In some experiments, the effect was slightly hypertensive. Intraventricularly, reserpine intensified pressor effects due to stimulation of a number of subcortical centers, especially those in the amygdaloid nucleus. The pressor reflex not changed by bilateral compression of

carotid arteries. When administered into the third ventricle, serotonin and, occasionally, reserpine evoked conspicuous waves of arterial blood pressure. They were not abolished by immobilization of the animal with gallamine triethiodide nor by artificial respiration.

Physiological Institute
Warsaw, Poland

034 Baruk, Henri. *La psychopharmacologie expérimentale chez les animaux et la prévention des accidents des nouveaux médicaments psychotropes.* (Experimental psychopharmacology in animals and the prevention of accidents with new psychotropic medication.) Bulletin de l'Académie Nationale de Médecine, 47:43-46, 1963.

Various aspects of animal experiments in psychopharmacology are discussed, and technical improvements are suggested. It is essential in animal experimentation to prolong studies and to observe the action of dose accumulation. It is also necessary to observe the effects of new drugs in a series of animals (i.e., fish, batrachians, reptiles, birds, and mammals), and to remember that rats are not good subjects for animal experiments because their extreme sensitivity to hypnosis can produce inaccurate results. It is emphasized that in psychopharmacology, the difference between biological experimentation and therapeutic use is an important factor.

rue Cassette
Paris, France

035 Lechat, P., Deleau, D., & Devillechabrolle, A. *Etude expérimentale du pouvoir protecteur de la pyridoxine vis-à-vis des effets toxiques de l'isoniazide.* (Experimental study of the protection of pyridoxine against toxic effects of isoniazid.) Therapie, 18(1):63-7, 1963.

The effects of pyridoxine hydrochloride on the LD₅₀ of isoniazid, the convulsant action of isoniazid, and on isoniazid-induced audiogenic seizures were observed. Pyridoxine hydrochloride in various concentrations increased the LD₅₀ of isoniazid in mice. The delayed convulsive seizures induced by toxic doses of isoniazid were not prevented in rats and rabbits, but the rate of mortality subsequent to the seizure was significantly reduced with simultaneous

administration of pyridoxine hydrochloride (2% to 4% i.p. in the rat and 2.8% and 5.6% i.v. in the rabbit). Pyridoxine hydrochloride did not change the sensitization of rats to audiogenic seizures produced by isoniazid.

Centre de Recherches de l'Association
Claude Bernard
Paris, France

2036 Clementi, Francesco & Zocche, Gian Paolo. *Morphological and pharmacological effects of reserpine, given alone or after iproniazid, on the catecholamines of the adrenal glands of the rat.* Journal of Cell Biology, 17:587-596, 1963.

Experiments were carried out in which the adrenal glands of 10 Sprague-Dawley rats (200 g) were examined at various intervals after treatment with 2.5 mg/kg s.c. of reserpine for 3 consecutive days (2 animals 4 hours after, 2 after 24 hours, 2 after 3 days, 2 after 6 days, and 2 after 9 days). Iproniazid (100 mg/kg i.v.) was given to four of the rats 4 hours before each treatment with reserpine. The adrenal glands were removed and one gland from each animal was immersed in 1% osmium tetroxide for 2 hours at 4° C, dehydrated, and examined under a Phillips EM 100A electron microscope. The contralateral gland was homogenized (20 mg gland/1 ml HCl solution) and injected i.v. into an adrenalectomized rat (24 hours previously) for biological assays of the amine content. After fixation with osmium tetroxide, the adrenomedullary cells were filled with well-formed granules that represent their catecholamine content. At 3 days after the beginning of reserpine treatment, these granules appeared to be emptied of their content and small vesicles containing dense deposits of catecholamines were seen. At 9 days after the beginning of treatment, the cells had attained a normal appearance. The submicroscopic structure of the adrenomedullary cells of the iproniazid-pretreated rats was similar to that of non-treated animals. The injection of medullary extract produced hypotension. It was concluded that the occurrence of the osmophilic, catecholamine-containing granules fragmented into smaller, finely scattered granules seen in animals treated with iproniazid and reserpine may represent an early stage of the reserpine effect.

University of Milan
Milan, Italy

- 2037 Gessa, G. L., Cuencat, E., & Costa, E. On the mechanism of hypotensive effects of MAO inhibitors. New York Academy of Sciences, 8:935-944, 1963.

The biochemical and pharmacological effects elicited at sympathetic nerve endings by MAO inhibitors, bretylium and by BW 392C60 (*N*-*o*-chlorobenzyl-*N*',*N*''-dimethylguanidine), a compound that exerts potent bretylium-like effects, are discussed. Cats, Sprague-Dawley rats, and New Zealand white rabbits were used. In all experiments, the rats were treated initially with an MAO inhibitor; 2 hours later were treated with 10 mg/kg of guanethidine i.p., and they were then killed. The decline in norepinephrine level produced by guanethidine was counteracted by bretylium, BW 392C60, harmaline, iproniazid, pargyline, phenelzine, and tranlylcypromine. Studies of the effects of BW 392C60 (1 to 10 mg/kg), bretylium (10 to 60 mg/kg), and iproniazid (5 to 25 mg/kg) on MAO activity and on the depletion of heart norepinephrine by guanethidine revealed that they prevent guanethidine from releasing heart norepinephrine. Studies of the effects of pretreatment of adrenalectomized cats with bretylium, BW 392C60 (10 mg/kg i.v.), pargyline (50 mg/kg i.p.), and phenelzine on hypertension induced by electrical stimulation of the distal end of the aplanchnic nerve showed a blocking response in all cases. Experiments on the effects of the drugs on hypertension induced by the action of DMPP (1,1-dimethyl-4-phenylpiperazinium iodide) showed that the drugs not only blocked but also reversed the hypertension. The bretylium-like action of MAO inhibitors appears to be independent of their action on MAO; in fact, blockade of the enzyme can be regarded as an undesirable side effect in their use as hypotensive agents.

Laboratory of Chemical Pharmacology
National Heart Institute
National Institutes of Health
Bethesda, Maryland

- 2038 Abramson, H. A., Gettner, H. H., Rolo, A., & Dean, G. Lysergic acid diethylamide (LSD-25): XXXIV. Comparison with effect of psilocybin on the Siamese fighting fish. Journal of Psychology, 56: 363-374, 1963.

The effects on Siamese fighting fish exposed to lysergic acid diethylamide (LSD-25) in the outside liquid with those fish injected with LSD-25 or with psilocybin are presented. Ten fish per jar were observed for 4 hours at varying concentrations of

LSD-25 (0.1, 0.5, and 1.0 mcg/ml) in the outside liquid. The LSD-25 was injected through the tail into the body cavity at doses of 0.01, 0.05, and 0.1 mcg; psilocybin was injected identically at doses of 2.5, 12.5, and 25.0 mcg. The nose up--tail down and Cartesian-diver positions were observed in all situations. The fish reacted to a much smaller amount of LSD-25 when it was administered by injection. Injected psilocybin affected the fish in the same way as the injected LSD-25, and the slopes of regression lines were almost identical. It is concluded that LSD-25 and psilocybin probably act on the same enzyme systems.

South Oaks Research Foundation, Inc.
Amityville, New York

- 2039 Griffiths, William J., Jr. Note on the effect of hydroxylamine on metrazol-induced fits in rats resistant and susceptible to audio-fits. Psychological Reports, 13:773-774, 1963.

The effects of hydroxylamine on metrazol-induced seizures among rats susceptible to and those resistant to sound-induced convulsions are reported. The subjects, 36 adult male and female albino rats, 18 of which were susceptible to audiogenic fits and 18 of which were resistant, were given metrazol, and the dose that was effective producing convulsions was determined for each rat. Hydroxylamine (75 mg/kg i.p.), followed in 90 minutes by the previously determined effective dose of metrazol, failed to protect 12 of 18 audio-susceptible animals from seizures. Only 3 of the 18 resistant rats continued to show the metrazol convulsion when pretreated with hydroxylamine.

(No address)

- 2040 Mietkiewski, Eugeniusz & Pryszczewska, J. O wyższej czynności nerwowej szczurów pod wpływem zmian poziomu serotoniny w mózgu. (Higher nervous functions in rats affected by raised or lowered serotonin levels in the brain.) Acta Physiologica Polonica, 8(1):115-124, 1962

Based on the Kotlarewski method, condition elementary reflexes were studied to determine the effect on higher nervous functions of raising or lowering serotonin levels in the brain. Fifteen white mice were used in the experiment. They were divided into several groups and treated as follows: (

proniazid 10 mg/kg i.v. The mice showed distinct and substantial disturbance of higher nervous functions. Their artificially elaborated conditional reflexes, trained for several hours, were weaker for a number of days, irregular and variably prolonged latency periods occurred, and differential inhibition was intensified. (2) Serotonin 10 mg/kg i.v. The effects were similar, but less pronounced than those in (1). (3) 5HTP 10 mg/kg i.v. with no MAO inactivation. The level of serotonin in the brain was gradually raised without previous inactivation of MAO. The disturbances of higher nervous functions were slightly less. (4) Iproniazid 100 mg/kg s.c. A slow rise in brain serotonin by MAO inactivation did not significantly modify the magnitude or the latency period of artificially elaborated conditional reflexes, but it distinctly intensified differential inhibition. (5) Reserpine 2 to 5 mg/kg s.c. There was pronounced and long-term lowering of brain serotonin level, causing relatively small changes in higher nervous functions. At the early stage of the reserpine action, when serotonin should have been released from cells but not yet eliminated, distinct and evident intensification of inhibition and modified artificial conditional reflexes occurred. Twenty-four hours later, i.e., after the elimination of serotonin, there was no significant abnormality in higher nervous functions.

Psychological Institute
Wroclaw, Poland

2041 Jones, Ann, de la Sierra, B. Gomez Alonso, & Trendelenburg, U. **The pressor response of the spinal cat to different groups of ganglion-stimulating agents.** *Journal of Pharmacology and Experimental Therapeutics*, 139(3):312-320, 1963.

The pressor response to 4-(*m*-chlorophenyl)-2-(*n*-butyl)-trimethyl-ammonium chloride (McN-A-343) and *N*-benzyl-5-(*α*-methyl-*γ*-pyrrolidyl acetate methobromide (AHR-602) was compared with that caused by two nicotinic substances, nicotine and dimethyl-phenylpiperazinium iodide (DMPP), in spinal cats (2 to 4 kg in weight) of both sexes. Intravenous injections of McN-A-343 and AHR-602 caused a transient fall and then a pronounced secondary rise of blood pressure. Ganglion block by depolarization, established by large amounts of nicotine or tetramethylammonium, abolished the pressor response; however, during the phase of nondepolarizing ganglion block by nicotine, McN-A-343 and AHR-602 caused a marked pressor response at

a time when nicotine and DMPP produced no response. The pressor response to McN-A-343 and AHR-602 was potentiated after large amounts of nicotine, and hexamethonium subsequently reduced the response to the expected control magnitude. Cocaine, morphine, and methadone reduced the blood pressure rise caused by McN-A-343 and AHR-602, but were ineffective against nicotine and DMPP. Block of transmitter release from adrenergic nerve endings by choline 2,6-dimethyl ether bromide also prevented the pressor response to McN-A-343 and AHR-602. It is concluded that the secondary rise of blood pressure caused by the intravenous injection of McN-A-343 and AHR-602 is due to an action of these agents on sympathetic ganglia. The McN-A-343 and AHR-602 resemble pilocarpine in their pharmacology and seem to produce stimulation of ganglia by an action on receptors different from those for nicotine and DMPP.

Harvard Medical School
Boston, Massachusetts

2042 Sigg, E. B., Soffer, L., & Gyermek, L. **Influence of imipramine and related psychoactive agents on the effect of 5-hydroxytryptamine and catecholamines on the cat nictitating membrane.** *Journal of Pharmacology and Experimental Therapeutics*, 142(1):13-20, 1963.

A study was made to determine whether the secondary amines of iminodibenzyls, iminostilbenes, and phenothiazines potentiate the cat nictitating-membrane response to norepinephrine (NE), epinephrine, and 5HT more than did the corresponding tertiary amines. Eighty-one cats (1.6 to 3.5 kg in weight) of either sex were used. Two to three doses of epinephrine (0.5 μg/kg to 4 μg/kg), NE (2 μg/kg to 32 μg/kg), and 5HT (10 μg/kg to 160 μg/kg) were given i.v. at approximately 5-minute intervals. All test amines were given i.v. into the femoral artery. Imipramine and desmethylinipramine (DMI) enhanced the nictitating membrane contraction in response to 5HT, NE, and electrical stimulation of the cervical sympathetic nerve. In acute experiments, imipramine potentiated 5HT more than did NE. The DMI was the most potent of the compounds studied in enhancing the response to NE. Prolonged pretreatment with imipramine resulted in preferential sensitization of the nictitating membrane to NE. Secondary amines of iminodibenzyls, iminostilbenes, dibenzocycloheptadienes and dibenzocycloheptatrienes having an *n*-propyl chain were more potent in enhancing the nictitating membrane response to NE than the corresponding tertiary amines. Structurally

related compounds that do not possess anti-depressant properties, or even CNS depressants, such as cyproheptadine, chlorpromazine, chlorpromazine, and promazine exhibited weak blocking action against NE and 5HT on the nictitating membrane, as does *N*-desmethylpromazine. Within the limited group of compounds studied, antidepressant activity appears to be correlated with the potentiation of the NE response on the nictitating membrane.

Geigy Research Laboratories
Ardsley, New York

- 2043 Somjen, G. G. & Gill, M. The mechanism of the blockade of synaptic transmission in the mammalian spinal cord by diethyl ether and by thiopental. *Journal of Pharmacology and Experimental Therapeutics*, 140(1):19-30, 1963.

This investigation was conducted in order to compare the effect of diethyl ether with that of a typical barbiturate on the mammalian spinal cord. Ventral root potentials were recorded in some experiments; in others, the response of single motoneurons before, during, and after administration of an anesthetic agent was studied by intracellular recording. Rats (300 to 400 g in weight) were used in experiments concerned with the effect of volatile anesthetics. An acutely decapitated cat was used in the comparison of the action of thiopental (40 mg/kg) with that of diethyl ether. Both drugs reversibly increased the voltage at which the propagated spike appears to depart from the synaptic potential, as shown by the ventral root records. In 15 out of 31 motoneurons, a reversible increase of the depolarization required to initiate an orthodromic impulse was shown by the intracellular records. The rate of rise of the synaptic potential was reduced on ventral root records, as well as on intracellular records, by anesthetics. No delay of the onset of the synaptic potential could be detected by either method of recording. Even though synaptic function was depressed by ether, no alteration of the antidromic spike in 25 out of 33 motoneurons was observed. The mechanisms of action of ether and thiopental could not be distinguished from each other by the methods employed in this study.

University of Otago
Dunedin, New Zealand

- 2044 Ehle, John Nelson. An analysis of the depressor and pressor effects of tryptamine in the chicken. *Journal of Pharmacology and Experimental Therapeutics* 139(1):31-37, 1963.

A study was made of both the depressor and pressor (post-MAO inhibitor) actions of tryptamine in the chicken. More than 100 chickens (weight range, 1.4 to 3.9 kg) of either sex and of various breeds were used in the experiments. Atropine (1 mg/kg in seven chickens, 10 mg/kg in three chickens) and methylatropine (1.0 mg/kg in 5 chickens) had no effect on the depressor action of tryptamine (200 mg/kg, i.v.), whereas the depressor effects of acetylcholine were totally blocked. Tolazoline (10.0 and 20.0 mg/kg) produced either no change or an increased depressor response to tryptamine. Phenoxybenzamine (5 to 15 mg/kg) blocked the depressor effect of tryptamine, and a pressor effect was unmasked. Phenoxybenzamine was chosen as the antihistaminic in preference to diphenhydramine. Cyproheptadine (200 µg/kg to 500 µg/kg) produced temporary blockade of the depressor response to tryptamine. Dihydroergotamine (1 to 4 mg/chicken) blocked the depressor and unmasked the pressor response to tryptamine. Dichloroisoproterenol (4 mg/kg) had no influence on the depressor action of tryptamine. The depressor action was reversed to a pressor action by 2 to 4 mg/kg i.v. of tranlylcypromine. These results indicate that tryptamine is a potent vasoconstrictor in the chicken. The specificity of tryptamine receptors in the chicken cardiovascular system is indicated by the fact that its vasoconstrictor action is not related to cholinergic or adrenergic mechanisms.

Pitman-Moore Company
Indianapolis, Indiana

- 2045 Zablocka, Barbara & Esplin, Don W. Central excitatory and depressant effects of pilocarpine in rats and mice. *Journal of Pharmacology and Experimental Therapeutics*, 140(2):162-169, 1963.

The anticonvulsant and excitatory effects of pilocarpine were studied in male adult rats (Sprague-Dawley) and male adult mice (CF #1) by means of electroshock seizures, spinal cord convulsions, pentylenetetrazol convulsions, and strychnine convulsions. Blood samples for determining changes in pH, plasma CO₂, and plasma electrolytes were taken from anesthetized rats. Pilocarpine 40 mg/kg s.c., produced an anticonvulsant

Effect against maximal electroshock seizures (MES), consisting of an early phase, with the peak effect being reached in 1 hour, and a weaker phase lasting more than 72 hours. The ED_{50} of pilocarpine at 1 hour after injection was 26 mg/kg. The anti-convulsant effect was weaker in mice and consisted only in prolongation of tonic extension with doses of pilocarpine up to 50 mg/kg. The drug markedly lowered EST in both rats and mice. Significant, but incomplete, antagonism of the effect of pilocarpine in rats was seen with 4 mg/kg of atropine. Complete antagonism of the effect of pilocarpine was observed in mice pretreated with 32 mg/kg of atropine. In both species, the CD_{50} of pentylenetetrazol was lower in pilocarpine-treated animals than in controls. Pilocarpine very markedly reduces the threshold for strychnine convulsions, and this effect is not prevented by pretreatment with atropine. Adrenalectomy in rats does not alter the effects of pilocarpine on MES, EST, or strychnine convulsions. The excitatory and depressant effects of pilocarpine appear to be due to direct central actions of the drug. Changes in blood pH, plasma CO_2 , and plasma electrolytes were slight after pilocarpine.

Department of Pharmacology
University of Utah
Salt Lake City, Utah

2046 Margolin, S., Plekss, O. J., & Fedor, E. J. Selective inhibition of dog spinal vasoconstrictor tracts by mebutamate. *Journal of Pharmacology and Experimental Therapeutics*, 140(2):170-178, 1963.

Pharmacodynamic experiments were performed in dogs and cats to determine the relations between the role of medullary vasomotor centers of the brain and of the spinal cord in the production of the hypotensive action of mebutamate. The following measurements were made: (1) trunk-to-limb cross circulation; (2) head-to-trunk cross circulation; (3) spinal locomotor reflexes; (4) spinal vasomotor reflexes; and (5) coronary peripheral resistance. Mebutamate selectively inhibited spinal vasoconstrictor tracts. The closely related compound meprobamate showed no inhibition of spinal vasoconstrictor tracts, although both drugs suppressed the spinal interneuronal arcs concerned with skeletal muscle motor function. The experiments confirmed the previously reported centrally acting mechanism for the hypotensive effect of mebutamate, and link this effect to a direct action on spinal vasomotor tracts and on the

brain stem vasomotor centers. Mebutamate greatly increased vascular limb flow when injected intrathecally in dogs, whereas meprobamate was ineffective. This concurred with cross circulation experiments demonstrating a marked vasodilatation of the isolated perfused limb, as evidenced by increased blood flow and reduced peripheral resistance. In similar trials, phenobarbital was found to be ineffective. The drop in peripheral resistance that followed the intrathecal mebutamate simulated that observed during spinal anesthesia. By direct comparison with lidocaine, it was shown that the spinal action of mebutamate was not due to a local anesthetic property of the drug. The data suggest that the spinal cord may play an important role in modulating the predominantly vasoconstrictor output from the medullary vasomotor regions.

Wallace Laboratories
Cranbury, New Jersey

2047 Hance, A. J., Winters, W. D., Bach-y-Rita, P., & Killam, K. F. A neuropharmacological study of gamma-aminobutyrylcholine, gamma-aminobutyric acid, physostigmine and atropine. *Journal of Pharmacology and Experimental Therapeutics*, 140(3):385-395, 1963.

Neocortical responses evoked in 26 unanesthetized, immobilized adult cats by stimulation of a variety of brain sites were studied for possible sensitivity to γ -aminobutyrylcholine (GABCh), GABA, physostigmine sulfate, atropine sulfate, and atropine methylnitrate. In addition, the effects of intraventricular administrations of GABCh, GABA, and physostigmine sulfate were compared in terms of alterations in affective behavior, in neurological symptoms, and in seizure patterns elicited by thiosemicarbazide (10 mg/kg i.p.). Differences between the actions of GABCh and those of GABA and physostigmine sulfate were as follows: (1) The i.v. administration of 1 to 10 mg/kg and topical application (0.1% to 5%) of GABCh to the neocortex failed to alter a variety of neocortical evoked responses. (2) The GABCh failed to interact with the effects of topically applied GABA (1% to 5%) on the same responses. (3) Intraventricular administration of a total dose of 30 mg of GABCh produced hyperexcitability, motor incoordination, a curious sulking behavior, and enhancement of the convulsive effects of thiosemicarbazide. The GABA in the same total dosage produced depression without motor incoordination and

mollified thiosemicarbazide seizures. Intraventricular administration of physostigmine sulfate (100 μ g) produced hyperexcitability, nondirected aggression without loss of motor coordination, with no demonstrable effects on the convulsive pattern produced by thiosemicarbazide. Atropine methylnitrate (0.5 to 5 mg/kg i.v.) caused no consistent changes in the EEG and minimal changes in the cortical evoked responses. Physostigmine sulfate (50 μ g/kg to 100 μ g/kg i.v.) in animals premedicated with atropine methylnitrate produced the characteristic low voltage EEG and had differential effects upon superficial cortical responses recorded from the medial suprasylvian and anterior sigmoid gyri. Atropine sulfate (0.5 or 1 mg/kg i.v.) produced the characteristic EEG pattern of high voltage, but had little or no action on the evoked responses.

University of California School of Medicine
Los Angeles, California

2048 McIsaac, Robert J. & Millerschoen, Nancy R. A comparison of the effects of mecamlamine and hexamethonium on transmission in the superior cervical ganglion of the cat. *Journal of Pharmacology and Experimental Therapeutics*, 139(1):18-24, 1963.

In order to investigate the mechanism of ganglionic blockade by mecamlamine, a quantitative comparison of the effects of hexamethonium (C-6) and mecamlamine on ganglionic transmission was undertaken. Cats of either sex, weighing between 2 and 3.5 kg, were anesthetized, and the vagus and cervical sympathetic nerves were dissected out. The relationship between dose and block of ganglionic transmission by C-6 and mecamlamine at high and low stimulus frequencies was investigated. An increase in frequency of stimulation from 2/second to 20/second had the same qualitative effect on the dose-response relationship for both drugs, and the maximum block attained was about the same in both cases. A greater blockade of ganglionic transmission at a high frequency of stimulation than at a low frequency was observed for mecamlamine (0.1 to 10 mg/kg) and hexamethonium (0.1 to 10 mg/kg) over a large part of the dose-response curve. Waning of tension occurred with continued stimulation during partial blockade with both hexamethonium (infusion of 25 μ g/kg min) and mecamlamine (30 μ g/kg min). The dose-response curve for stimulation of the ganglion by intra-arterial administration of acetylcholine was shifted to the right by constant infusion of either hexamethonium

(25 μ g/kg min) or mecamlamine (30 μ g/kg and 60 μ g/kg min). When hexamethonium (15 μ g to 30 μ g), acetylcholine (100 μ g to 250 μ g), or tetraethylammonium (200 μ g) was given simultaneously with mecamlamine (10 μ g to 20 μ g), the total blocking effect was less than that with mecamlamine alone.

Department of Pharmacology
State University of New York
Buffalo, New York

2049 Weil-Malherbe, H. & Posner, Herbert. The effect of drugs on the release of epinephrine from adrenomedullary particles in vitro. *Journal of Pharmacology and Experimental Therapeutics*, 140(1):93-102, 1963.

The spontaneous and drug-induced release of particle-bound epinephrine in 600-g supernates of rabbit adrenal glands has been studied in media of varying compositions. Releasing effects were studied in an isotonic solution containing 0.125 M potassium chloride, 0.005 M potassium phosphate of pH 6.5, and 0.006 M magnesium chloride at 25° C. The inhibition of release was studied in 0.3 M sucrose at 37°. Reserpine and chlorpromazine caused practically complete release at 10⁻⁴ M within 30 minutes, and prochlorperazine, thioridazine, trifluoperazine, and trifluorpromazine were approximately as active. Promazine, promethazine, and methylene blue were less active as agents of release. Imipramine possessed some activity, but less than chlorpromazine. Out of 50 drugs chemically unrelated to reserpine and the phenothiazines, only 3 were found to have strong releasing activity at 2 x 10⁻⁴ M: p-chloromecuribenzoate, sodium deoxycholate, and suramin sodium. Tranquilizers and sedatives not belonging to the phenothiazine series showed no releasing activity. The in vivo inhibition of the releasing effect of reserpine by MAO inhibitors could not be duplicated in vitro. No potentiation or inhibition was observed with combinations of releasing agents with each other or with inactive compounds. Reserpine (10⁻⁵ M) and several of the phenothiazines were found to inhibit the spontaneous release of particle-bound epinephrine.

Saint Elizabeths Hospital
Washington, D. C.

2050 Furchgott, Robert F., Kirpekar, S. M., Rieker, Maria, & Schwab, Albert. **Actions and interactions of norepinephrine, tyramine and cocaine on aortic strips of rabbit and left atria of guinea pig and cat.** *Journal of Pharmacology and Experimental Therapeutics*, 142(1):39-58, 1963.

The actions and interactions of norepinephrine (NE), tyramine, and cocaine were studied on strips of thoracic aorta from rabbits and on electrically driven left atria from guinea pigs. Data on the following are reported: (1) potentiation of the response to NE and antagonism of the response to tyramine by cocaine on aortic strip; (2) the effect of cocaine on dose-response curves to NE and tyramine in the aortic strips and atria; (3) potentiation of the response to NE by cocaine and tyramine and the lack of antagonism by cocaine of the response to a high dose of tyramine on reserpinized aortic strips; (4) restoration of the tyramine response in reserpinized aortic strips following incubation of the strips with NE (repletion); (5) antagonism of the tyramine response by cocaine on reserpinized aortic strips following incubation of the strips with NE; (6) potentiation of the response to NE and supramaximal voltage stimulation and antagonism of the tyramine response by cocaine on atria; (7) potentiation of NE response by cocaine and tyramine on reserpinized atria; and (8) restoration of positive inotropic response to tyramine and cocaine on reserpinized atria following incubation of the atria with NE. Experimental findings are discussed in conjunction with the recent findings of others. A hypothetical scheme is developed for the relationship between effector cells and structures, possibly presynaptic nerve terminals, that remove NE either by storage or by enzyme inactivation.

Downstate Medical Center
Brooklyn, New York

2051 Sanner, Erland. **Tubular excretion of dopamine (3-hydroxytyramine) by the chicken kidney.** *Acta Physiologica et Pharmacologica*, 20(4):375-384, 1963.

Information was obtained on the mechanism of dopamine excretion by the kidney of Rhode Island Red chickens (2 years old, 1.9 to 2.8 in weight). Dopamine (50 μ g to 150 μ g) was injected into the leg vein of the chickens. All birds were pretreated with an MAO-inhibitor (nialamide 100 mg/kg i.v. or JB-6 10 mg/kg i.v.). Dopamine was found to be excreted unilaterally in excess on the

dopamine injected side. Tolazoline (5 mg i.v.) given simultaneously with dopamine inhibited the excretion of dopamine. Probenecid (50 mg/kg i.v.) given 20 minutes before i.v. injection of dopamine and phenol red produced strong inhibition of phenol red excretion, but left dopamine transport unchanged. Dopamine did not show any significant influence on the glomerular filtration rate. These observations indicate that the most probable excretion mechanism of dopamine is tubular secretion involving the common base transport system.

University of Uppsala
Uppsala, Sweden

2052 Johannesson, Torkell & Schou, Jens. **Analgesic activity and brain concentration of morphine in tolerant and non-tolerant rats given morphine alone or with neostigmine.** *Acta Pharmacologica et Toxicologica*, 20(3):213-221, 1963.

A method for measuring degree of analgesia has been used to compare the analgesic potency of morphine in tolerant and non-tolerant rats. In adult, male, albino rats (130 to 220 g in weight) at the ED₅₀ level (0.1 mg/kg i.p.), morphine was about three times more potent in nontolerant than in tolerant animals. Neither in nontolerant nor in tolerant rats did i.p. injection of neostigmine (0.1 mg/kg) immediately after morphine alter the analgesic response. The concentration of morphine found in the brains 30 minutes after i.p. injection of 10 mg/kg morphine did not differ between tolerant and nontolerant rats. Neostigmine (0.1 mg/kg i.p.) administered simultaneously with the morphine injection did not alter the concentrations of morphine in the brain. Reserpine (1 mg/kg i.p.) 3 to 5 hours before morphine did not alter the analgesic response in nontolerant rats.

University of Copenhagen
Copenhagen, Denmark

2053 Johannesson, Torkell & Schou, Jens. **Morphine and normorphine in the brains of rats given identically analgesic doses of morphine, codeine or normorphine.** *Acta Pharmacologica et Toxicologica*, 20(2):165-173, 1963.

An analgesimetric procedure on adult, male, albino rats of a single strain (140 to 230 g in weight) was employed to compare the analgesic potencies of morphine, codeine,

and normorphine. Nine groups of rats, each group consisting of 30 to 50 animals, were given morphine in doses of 2.5, 5.0, or 10 mg/kg i.p., and codeine and normorphine were given in doses of 10, 20, or 40 mg/kg i.p. Morphine was found to be 3.3 and 6 times more potent than codeine and normorphine, respectively. From the dose-response curve, identically analgesic doses of the three drugs were chosen that would be expected to produce 37.5% and 70% analgesia. At these dose levels (5 and 8.5 mg/kg for morphine, 16 and 30 mg/kg for codeine, and 28 and 51 mg/kg for normorphine), the concentrations of morphine in the brain were in the same range, whether analgesia was produced by morphine or by codeine (0.19 µg/g to 0.24 µg/g on the average). These results indicate that codeine is O-demethylated into morphine before exerting its analgesic effect. The concentration of normorphine in the brain was four to five times higher than that of morphine. These results invalidate the hypothesis that morphine analgesia is due to normorphine.

University of Copenhagen
Copenhagen, Denmark

- 2054 Johannesson, Torkell & Norn, Svend.
The effect of morphine on the histamine contents of brain and skin in the rat. *Acta Pharmacologica et Toxicologica*, 20(2):158-164, 1963.

The effect of compound 48/80, polymyxin B, and morphine on the histamine contents of the brain and skin of rats was investigated, and the histamine-releasing capacities of these substances were studied in vitro in a suspension of mast cells derived from rat peritoneum. Adult, male, albino rats (130 to 220 g in weight) were used for these experiments. In seven rats given compound 48/80, 22 mg/kg i.p. in 7 doses over 4 days, and in five rats given polymyxin B, 35 mg/kg i.p. in 6 doses over 4 days, the histamine contents of the skin were reduced by 75% and 70%, respectively; the histamine contents of the brain were not affected. Morphine did not reduce the histamine contents of the brain or skin, whether it was administered repeatedly by s.c. injection or by a single 150 mg/kg i.p. injection. In the mast-cell suspension, morphine (100 µg/ml) released 39% of the total amount of histamine, whereas 0.5 µg/ml of compound 48/80 or polymyxin B released 72% and 66%, respectively. The results indicated that morphine releases histamine only at high concentrations, and that neither morphine

tolerance nor the analgesic action of morphine is connected with histamine liberation.

University of Copenhagen
Copenhagen, Denmark

- 2055 Karandikar, S. M., Joglekar, G. V., Chitale, G. K., & Balwani, J. H.
Protection by indigenous drugs against hepatotoxic effects of carbon tetrachloride—a long term study. *Acta Pharmacologica et Toxicologica*, 20(3):273-280, 1963.

The long-term effects of LIV-52, an Indian indigenous proprietary medicine, and of promethazine against the hepatotoxic effects of carbon tetrachloride were investigated in rats. Albino female rats (3 groups of 10 rats each), weighing 150 to 180 g, were given carbon tetrachloride (0.2 ml mixed with 0.2 ml paraffin) s.c. twice each week. One group received promethazine (2.5 mg/rat) daily intragastrically; the second group received LIV-52 (30 mg/rat); and the third group received no protective agent. Another group of 10 rats was used as a control. Eight male rabbits, weighing 1.5 to 1.8 kg, also received carbon tetrachloride (1 ml 1 ml liquid paraffin) s.c. twice each week. Six of these received 2 g of LIV-52 daily by intragastric tube. The LIV-52 prolonged the survival time in both rats and rabbits and also reduced, to a considerably large degree, the percentage mortality in rats due to carbon tetrachloride than did promethazine. The LIV-52 produced no alteration in size and volume of liver, whereas promethazine showed an increase in volume without a corresponding increase in weight. The lobulation seen in the carbon tetrachloride and promethazine group was not observed in the LIV-52 group. The mechanism of the protective effect of LIV-52 is not known.

B.J. College
Poona 1, India

- 2056 Larsen, Valdemar. The teratogenic effects of thalidomide, imipramine HCl and imipramine-N-oxide HCl on white Danish rabbits. *Acta Pharmacologica et Toxicologica*, 20(3):186-200, 1963.

The teratogenic effects of thalidomide, imipramine HCl, and imipramine-N-oxide HCl were investigated in 40 female Danish White

country Breed rabbits. The rabbits were tested, and 14 were given 100 mg/kg of alidomide s.c. daily for the following periods: four rabbits from 1 to 17 days after mating, six rabbits from 3 to 20 days after mating, and four rabbits from 6 to 20 days after mating. Imipramine HCl, 15 mg/kg s.c. daily was given to six rabbits from 3 to 20 days after mating, and 15 mg/kg s.c. daily was given to four rabbits from 3 to 18 days after mating. Imipramine-*N*-oxide HCl was given from 3 to 18 days after mating to six rabbits receiving 25 mg/kg s.c. daily and to four rabbits receiving 15 mg/kg s.c. daily. A 0.9% saline solution was given to six control rabbits from 3 to 20 days after mating. Macroscopic examination showed that 21 of the 35 young of alidomide-treated rabbits were abnormal in some way (malformed paws, extremely short tail, only one kidney, or no kidneys). In the imipramine HCl-treated rabbits' young, 1 out of 53 had an extremely short tail, and 1 out of 59 in the imipramine-*N*-oxide HCl had only one kidney. No young from the control group of 25 were abnormal. The effect of thalidomide depended on time between mating and beginning administration. Thalidomide reduced the fertility, but the imipramine compounds, in the doses given, did not.

Imex, Ltd.
Copenhagen, Denmark

2057 Frey, H. H. **Monoamine oxidase inhibition and sensitivity of the nictitating membrane to noradrenaline.** *Acta Pharmacologica et Toxicologica*, 20: 281-285, 1963.

The effect of MAO inhibition on the sensitivity of the nictitating membrane of the cat to noradrenaline was studied in order to explain any possible role of the enzyme in the inactivation of catecholamines at the receptor. A group of 10 cats received iproniazid (50 mg/kg i.p.); another group of 5 cats received iproniazid (40 to 60 mg/kg i.p.); and 10 cats (controls) received no pretreatment. About 20 to 24 hours after the injection of iproniazid, the decentralized nictitating membranes of the pretreated cats were more sensitive to noradrenaline (0.5, 1.0, 2.0, 4.0, and 10.0 µg/kg) than were those of the controls. The reaction of the decentralized membrane of the iproniazid-treated group to cocaine (1.0 mg/kg), tyramine (0.1 mg/kg), and nialamide (25.0 µg/kg) was also greater than that of the controls. The reactions of

iproniazid-pretreated cats were smaller than those of the controls. Denervation of the nictitating membranes showed a trend toward slightly higher reactions in the iproniazid group.

Leo Pharmaceutical Products
Ballerup, Denmark

2058 Jóhannesson, Torkell. **Effect of morphine on tolerance to nalorphine and its metabolism.** *Acta Pharmacologica et Toxicologica*, 20(4):281-285, 1963.

These experiments were conducted to determine whether or not morphine-tolerant rats are also tolerant to nalorphine and whether simultaneous injections of the two drugs increase the amounts of nalorphine found in the brain. Adult, male, albino rats (140 to 250 g in weight) were used. Twelve nontolerant rats died 14 to 110 minutes after i.p. injections of nalorphine (360 mg/kg), whereas eight morphine-tolerant rats survived at least 24 hours after an identical injection. Nalorphine concentration was higher in the brains of the nontolerant rats than in those of the morphine-tolerant rats. Morphine (360 mg/kg i.p.), nalorphine (150 mg/kg i.p.), or these quantities of morphine and nalorphine simultaneously were given to three groups, each consisting of six rats. After 30 minutes, nalorphine was found at higher concentrations in the brains when given with morphine than when given alone. Morphine was found at concentrations within the same range, whether given alone or with nalorphine.

University of Copenhagen
Copenhagen, Denmark

2059 Carlsson, Arvid & Waldeck, Bertil. **β-Hydroxylation of tyramine in vivo.** *Acta Pharmacologica et Toxicologica*, 20(4): 371-374, 1963.

The mode of action of tyramine has been investigated in vivo. To determine the uptake of tyramine and its metabolite octopamine, mice (20 g) were injected i.v. with C¹⁴-tyramine (0.1 mg/kg). Tyramine was taken up by both the heart and femoral muscle and rapidly converted to octopamine. The heart was found to have a higher capacity for the forming and storing of octopamine. Pretreatment with nialamide (100 mg/kg i.p.) 2 hours before C¹⁴-tyramine resulted in the recovery of much larger amounts of both tyramine and octopamine. In rats, C¹⁴-tyramine was recovered in larger

amounts in the denervated than in the intact submaxillary gland. In mice after reserpine treatment (10 mg/kg i.p., 6 hours before C^{14} -tyramine), the accumulation of tyramine and octopamine in the heart was suppressed and tyramine in the femoral muscle was reduced. Guanethidine (50 mg/kg i.p. 1 hour before C^{14} -tyramine) showed the same effect on octopamine but had a smaller effect on tyramine uptake. The effects of reserpine and guanethidine were much less pronounced when the MAO was inhibited by nialamide. These results support the existence of both intraneuronal and extraneuronal binding sites of tyramine.

University of Göteborg
Göteborg, Sweden

- 2060 Kopeloff, Lenore M. & Chusid, Joseph G. **Convulsant effect of hydroxylamine in epileptic monkeys and rats.** Proceedings of the Society for Experimental Biology and Medicine, 112(2):306-308, 1963.

This study was undertaken to investigate the clinical responses of epileptic and non-epileptic monkeys and rats to injection of hydroxylamine. Four monkeys made chronically epileptic by cerebral application of alumina cream through multiple injections or insertion of an alumina disc were more susceptible to the early convulsant effects of hydroxylamine (7.5 mg/kg i.v.) than four normal or four operated nonepileptic monkeys. Five of nine male, Sherman rats made chronically epileptic by local cerebral cobalt application developed clinical seizures within 1 to 5 minutes after i.v. injection of hydroxylamine (5 mg/kg), and all nine showed seizures after pentylenetetrazol (20 mg/kg i.m.). None of the normal, unoperated controls developed seizures after either test. The early convulsant effects were associated with physiological changes, such as hyperpnea and methemoglobinemia, and these changes were shown to be unrelated to brain GABA levels in rats.

New York Psychiatric Institute
New York, New York

- 2061 Chen, Graham. **A study of convulsants under the influence of reserpine and α -benzoylamino- β -(3-pyridyl) acrylic acid piperidide.** Proceedings of the Society for Experimental Biology and Medicine, 112(2):306-308, 1963.

The influence of reserpine and α -benzoylamino- β -(3-pyridyl) acrylic acid piperidide

(BA3P) upon the response of mice to the convulsive action of 19 drugs has been investigated. Male, albino mice of Webster strain (18 to 24 g in weight) were given reserpine (4 mg/kg i.p.) 4 hours before the convulsant or BA3P (167 mg/kg i.p.) one-hour before the convulsant. Reserpine was found to facilitate tonic extensor seizure induced by the following drugs: hexahydro-2'-methylspiro[cyclohexane-1,8'(6H)-oxazin[3,4-A]pyrazine] (COP) 0.1 mg/kg i.v.; α -benzoylamino- β -(4-pyridyl) acrylic acid piperidide (BA4P) 0.5 mg/kg i.v.; caffeine 1.0 mg/kg i.v.; bulbocapnine 1.5 mg/kg i.v.; 4,4,4-trichloro-3-hydroxy-N-(2,2,2-trichloro-1-hydroxyethyl) butyramide (THBA) 7 mg/kg i.p.; bemegride 0.25 mg/kg i.v.; $\alpha,\alpha,\beta,\beta$ -tetramethyl succinimide (PM-1090) 0.1 mg/kg i.v.; camphorimide 40 mg/kg i.m.; 1,5,5-trimethyl-2,4-dithiohydantoin (TMTH) 6 mg/kg i.m.; nikethamide 1.5 mg/kg i.v.; pentylenetetrazol 0.5 mg/kg i.v.; N-isopropyl bicyclo (2,2,1)-5-heptene-2,3-dicarboximide (IDCI) 60 mg/kg i.p.; 17- β -dimethylamino-5-androsten-3 β -ol (DMAA) 40 mg/kg i.m.; and hexahydro-1-isopropyl-2(3H)-benzimidazolone $\cdot$ H₂O (IPBI) 120 mg/kg i.p. Reserpine did not affect the tonic extensor seizures induced by strychnine (0.005 mg/kg i.v.), picrotoxin (0.15 mg/kg i.v.), hydralazine (1.0 mg/kg i.v.), 5,7-diphenyl-1-3-diazadimantan-6-ol (1757 I.S.) 0.008 mg/kg i.v., or 10-(2-dimethylaminopropyl)-acridone (DAPA) 0.05 mg/kg i.v. The BA3P potentiated convulsions induced by strychnine (0.16 mg/kg i.m.), 1757 I.S. (1.48 mg/kg i.m.), COP (30.0 mg/kg i.m.), BA4P (21.60 mg/kg i.m.), and picrotoxin (14.50 mg/kg i.m.), whereas it suppressed the action of hydralazine (164.0 mg/kg i.m.), PM-1090 (11.0 mg/kg i.m.), camphorimide (28.0 mg/kg i.m.), TMTH (3.88 mg/kg i.p.), nikethamide (385 mg/kg i.m.), pentylenetetrazol (74.0 mg/kg i.m.), IDCI (78.0 mg/kg i.p.), and DMAA (25.0 mg/kg i.p.); BA3P produced no effect on the action of DAPA (22.7 mg/kg i.m.), caffeine (360.0 mg/kg i.m.), bulbocapnine (146.0 mg/kg i.m.), THBA (28.7 mg/kg i.p.), bemegride (25.5 mg/kg i.m.), and IPBI (68.0 mg/kg i.p.).

Parke, Davis & Company
Ann Arbor, Michigan

- 2062 Fujimoto, James M., French, Ronald Graham, John K., & Inturrisi, Charles E. **Effects of levorphanol and levallorphan on osmolality of serum from water-loaded rats.** Proceedings of the Society for Experimental Biology and Medicine, 114(1):193-195, 1963.

Changes in the osmolality of the serum of water-loaded rats treated with the anti-diuretic levorphanol and the effect of

vallorphan, an antagonist, on these changes were studied. Fasted male Sprague--wley rats (200 to 300 g in weight) were gavaged orally with tap water (5% of body weight) and then injected s.c. with one of the following treatments: (1) distilled water, 35 rats; (2) 3 mg/kg levorphanol, 30; (3) 5 mg/kg levorphanol, 29; (4) 3 mg/kg levorphanol and 1 mg/kg levallorphan, 19; (5) 3 mg/kg levorphanol and 5 mg/kg levallorphan, 19; (6) 5 mg/kg levorphanol and 1 mg/kg levallorphan, 20; or (7) 5 mg/kg levallorphan, 18. To determine total water content of the stomach and small intestine, fasted female rats were gavaged with tap water and then injected as follows: (1) distilled water, 5 rats; (2) 3 mg/kg levorphanol, 5; (3) 5 mg/kg levorphanol, 5; or (4) 5 mg/kg levorphanol and 10 mg/kg levallorphan, 5. Levorphanol altered the control serum osmolality response to the 5% saline water load in rats. The change at a low dose of levorphanol was consistent with retention of water systemically, due to the antidiuretic effect of levorphanol. At a high dose, another component appeared in the osmolality curve, suggesting that inhibition of water absorption from the gastrointestinal tract was occurring. When the water content of stomach and intestines was measured, the only significant difference from controls was found for the 5 mg/kg dose of levorphanol. All effects of levorphanol were antagonized by levallorphan.

Louisiana State University School of Medicine
New Orleans, Louisiana

2063 Miller, Zelma B. & Pasciuto, Mary C.
Lethal effect of chlorpromazine on the chick embryo. Proceedings of the Society for Experimental Biology and Medicine, 114(2):436-439, 1963.

The lethal effect of chlorpromazine on the development of the chick embryo is described. The yolk sac of fertile White Leghorn eggs was injected with 0.9 or 1.8 mg of chlorpromazine just prior to or at intervals after incubation of the eggs at 37°C. Control eggs were injected with 2 ml sterile saline. Both doses of the drug were toxic, and chlorpromazine was found to be most destructive if administered within the first 48 hours of incubation. At 72 hours, there was little effect, and chlorpromazine had no effect at 96 hours. At 17 days, the average weight of embryos treated with 1.8 mg chlorpromazine (at 48 hours) was 13.3 g as compared with 16.7 g for the controls. Gross defects, such as

absence of eyes or decreased pigmentation, were noted more frequently in the treated embryos than in the controls.

Harvard School of Public Health
Boston, Massachusetts

2064 Foote, R. H. & Gray, L. C. **Effect of tranquilizers on libido, sperm production and in vitro sperm survival in dogs.** Proceedings of the Society for Experimental Biology and Medicine, 114(2):396-398, 1963.

The effect of chlorpromazine and promazine on the reproductive function in male beagle dogs, weighing from 9 to 11 kg, is discussed. In vitro studies of the effect on sperm motility of chlorpromazine and promazine (2, 20, 100, 200, and 2,000 µg/ml) showed no drug effect at concentrations below the 200 µg/ml level. Higher levels were spermicidal. Oral administration of chlorpromazine (4.4 mg/kg) to eight dogs every other day for nine days did not reduce the libido of dogs trained to routine semen-collection procedures. The drug treatment had no effect on sperm motility. The percentage of motile cells surviving storage in samples collected prior to treatment and during the various intensities of chlorpromazine administration did not differ significantly. There was no consistent effect of chlorpromazine upon sperm output. It would appear, therefore, that 4.4 mg/kg of chlorpromazine did not alter the normal hypothalamic--pituitary--gonadal relationships in these dogs.

Department of Animal Husbandry
New York State College of Agriculture
Cornell University
Ithaca, New York

2065 Woods, James W. & Ajzen, Horacio.
Effect of reserpine and guanethidine on excretion of 3-methoxy-4-hydroxymandelic acid in man. Proceedings of the Society for Experimental Biology and Medicine, 114(1):107-109, 1963.

Large i.v. doses of reserpine and guanethidine were administered to human subjects, and urinary 3-methoxy-4-hydroxymandelic acid (VMA) was measured in order to seek evidence

for or against release of catecholamines from body depots and subsequent increased excretion, and to compare the effects of the two drugs. Sixteen normal volunteers and 16 volunteers with essential hypertension were given reserpine (average, 4.5 mg/subject) by i.v. infusion or guanethidine (average, 31 mg/subject) by i.v. infusion. Neither drug produced a statistically significant change in VMA excretion. These results may indicate that tissue depletion did not occur, but if depletion did occur, it was not due to release of catecholamines by tissue stores but to interference with the synthesis of these substances (norepinephrine and epinephrine) or by blocking storage of these substances.

University of North Carolina
School of Medicine
Chapel Hill, North Carolina

2066 Greene, Frank E. Absence of a renal effect from two substituted propanediols: Meprobamate and mebutamate. Proceedings of the Society for Experimental Biology and Medicine, 114(1):165-168, 1963.

To determine whether the hypotensive effects of meprobamate and mebutamate are related to a renal action, either electrolytic or hemodynamic studies, using conscious beagles of both sexes, were carried out. Water was withheld 24 hours prior to the experiment and 20 ml/kg of tap water was given by stomach tube at the start of the experiment. Glomerular filtration rate (GFR) measured by the clearance of inulin, renal plasma flow measured by p-aminohippurate clearance (PAH), and chloride, sodium, and potassium determinations were made. Doses ranging from 1 to 90 mg/kg of meprobamate i.v. were administered, following which the urine flow, pH, and electrolyte output were measured. Chlorides were determined for all samples, but sodium and potassium were measured for the highest dose only. No changes were detected in any of the electrolytes, regardless of dose. A delayed onset of CNS effect was observed, but no renal effect was noted. Clearance of inulin and PAH were measured using 30 mg/kg of meprobamate and 20 mg/kg of mebutamate. Neither clearance was affected by meprobamate, and only a small reduction occurred in PAH clearance following mebutamate. Electrolytes, pH, and flow were also measured following doses of 10 to 50 mg/kg of mebutamate. The electrolytes were not

affected by this drug. It was concluded that these compounds are without significant renal effects.

University of Florida
College of Medicine
Gainesville, Florida

2067 Horn, Leif & Converse, John Marquis. Chlorpromazine in protection from acute effects of extensive high temperature skin injury in rats. Proceedings of the Society for Experimental Biology and Medicine, 113(1):194-197, 1963.

Chlorpromazine was used in the treatment of severe skin burns in rats to test the theory that drug interference with metabolism after a lethal burn might decrease mortality rate in the subsequent shock phase. Four hundred young adult, male, albino Wistar rats (250 to 300 g in weight) were divided into five treatment groups: Group I—no treatment, standard laboratory environment (16° to 28° C, high humidity); Group II—no treatment, controlled temperature (20° C) and humidity (40%); Group III—fluid therapy; Group IV—fluid therapy plus 1.5 mg/kg chlorpromazine; and Group V—fluid therapy plus 0.5 mg/kg chlorpromazine. Burned rats were extremely sensitive to environmental conditions; a substantial increase in survival was afforded by controlling humidity and temperature. Fluid therapy increased survival at 24 and 48 hours, but 10-day survival was only moderately increased. The immediate lethal consequences of burn shock were nullified by both doses of chlorpromazine, but when given for 48 hours or longer, chlorpromazine increased mortality.

New York University School of Medicine
New York, New York

2068 Bhussry, B. R. & Rao, Saroja. Effect of sodium diphenylhydantoinate on oral mucosa of rats. Proceedings of the Society for Experimental Biology and Medicine, 113(3):595-599, 1963.

The effect of systemic administration of sodium dilantin on the oral mucosa of rats was investigated. Five litters, each of newborn albino rats, were used. At 3 days of age, eight rats in each litter were given 100 mg/kg dilantin i.p., and this dosage

continued at 3-day intervals until up to five doses had been given; the remaining control animals received saline. Animals were sacrificed 6 days after their last injection. Oral mucosa from the cheeks was processed by routine histological procedures. Dilantin caused a significant increase in keratinization of the oral epithelium. Connective tissue of oral mucosa showed elevated fibroblastic activity with pronounced collagen fiber formation. Histochemical staining reactions suggested a substitution of glycoproteins for mucopolysaccharides in the epithelial cell layers. Increase in the glycoprotein and mucopolysaccharide staining materials in the connective tissue was noted. This investigation suggested a relation between the severity of microscopic changes in the oral mucosa and dose and duration of dilantin therapy.

Forgetown University School of Medicine and Dentistry
Washington, D. C.

2069 Reiniš, S. Vliv narkózy na mozkové pulsace a pO_2 v mozkové kůře u králíků. (The effect of anesthesia on brain pulsations and cerebral cortex pO_2 in rabbits.) *Activitas Nervosa Superior*, 5: 185-186, 1963.

The experiments were performed on eight adult rabbits in which electrodes were inserted in the parietal bone 4 to 6 weeks before the test. Brain pulsations were registered by a plethysmograph, and oxygen tension was recorded by a platinum electrode connected to the potentiometer of a polarograph. Changes in polarization were registered by a reflecting galvanometer on an oscillograph. Allobarbitol (approximately 0.9 ml of 10% solution per kg body weight) was injected through the ear vein until the corneal reflex disappeared. During administration of the narcotic, the oxygen tension in the cerebral cortex gradually dropped below the initial value, but it quickly returned to, and remained at, the original value to the end of narcosis. During the drop in oxygen tension, the brain pulsation remained at approximately the initial value, with temporary rise or fall double that of the initial value. The fall in oxygen tension is probably caused by a temporary increase in oxygen demand and possibly by a definite, transitory disruption of blood supply to the brain. Return to normal oxygen tension is accompanied by

increased pulsation. When the oxygen tension regains its initial value, the brain pulsations again drop. This may explain the depressed metabolism of brain tissue during narcosis.

Charles University
Plzeň, Czechoslovakia

2070 Sobotka, P., Mysliveček, J., Hassmannová, J., & Záhlava, J. Vliv některých látkových a fyzikálních faktorů na elektrickou aktivitu mozku za vývoje. (The effect of some drugs and physical factors on the development of electrical activity in the brain.) *Activitas Nervosa Superior*, 5: 187-188, 1963.

The effect of acetylcholine (ACH) on spontaneous electric activity of the brain was studied in rats 5 to 30 days old and in mature rats. Filter paper soaked in 10% ACH was applied to the dura mater of adult rats under diallyl barbituric acid narcosis (40 mg/kg). After 8 to 20 minutes, deviations of the high-voltage and fast-frequency tracings were noted, which continued for several minutes after the filter paper was removed and the dura was washed with Ringer solution. Local application of 1% ACH had no effect. This effect could be produced by 10% ACH in narcotized rats of up to 25 days of age. The 10% ACH solution had no effect on narcotized young rats. In waking rats 15 to 30 days old, 10% ACH produced increased fast-wave activity after 2 to 5 minutes. The 10% ACH solution damped activity in 5-day-old rats, whereas 1% ACH solution increased the activity. A weak stream of physiological solution, at about the temperature of ice, when applied to the cortex resulted in smoothing out of the evoked potential (EP) produced by stimulation of the thalamic auditory cortex with electric impulses (25 V, 50 μ sec to 200 μ sec). The duration of this effect was determined by the intensity of the cooling. In experiments on cats and rats, it was found that cooling selectively suppresses the cortical component of the EP. Cooling lengthened the latency of response, and the effects of cold were also more pronounced in the more mature animals.

Charles University
Plzeň, Czechoslovakia

2071 Michelson, M. J. **Pharmacological evidences of the role of acetylcholine in the higher nervous activity of man and animals.** *Activitas Nervosa Superior*, 3:140-147, 1961.

A variety of experiments in animals and humans is reported, providing evidence concerning the role of acetylcholine in the higher nervous system. The experiments are grouped under two topic headings: (1) the antagonism between cholinopositive and cholinonegative drugs; and (2) the antagonism between cholinonegative and adrenergic drugs. Atropine, parpanite, and other cholinolytics reversibly damage the higher nervous activity in men and the conditioned reflexes in animals. This action is reversed partly or entirely by the anticholinesterases, such as eserine, prostigmine, and paraoxon. Paraoxon and the cholinomimetics, nicotine and arecoline, accelerate the formation of new conditioned reflexes, but atropine and parpanite antagonize this formation. The anticholinesterases reinforce the processes of internal inhibition (differentiation, extinction); the cholinolytics weaken them. The action of cholinolytics is inhibited by amphetamine, which is adrenergic. Quaternary derivatives of cholinolytics and cholinomimetics that cannot penetrate from the blood into the brain have no influence on higher nervous activity, but their action on the peripheral cholinoreceptors is usually more pronounced than that of the corresponding tertiary amines.

Academy of Sciences
Leningrad, U.S.S.R.

2072 Chaloupka, Z. & Mysliveček, J. **Farmakologické a fyzikální ovlivnění tzv. dočasného osvojení rytmu evokovaných korových potenciálů. (Pharmacological and physical modification of the so-called temporary acquiring of rhythm in evoked cortical potentials.)** *Activitas Nervosa Superior*, 5:184-185, 1963.

Research concerning the phenomenon of the "temporary acquiring of rhythm in evoked cortical potentials" was carried out on adult rats, using 5-second-duration sound waves of 5- to 8-cycle frequencies as stimuli. The 5-cycle frequency gave the best results. The same phenomenon can also be evoked by administering chloralose, urethane, and allobarbitol. Not all of the

rats reacted to these treatments. In the case of chloralose and urethane narcoses, the phenomenon can be successfully evoked by sound stimuli higher than that of allobarbitol frequency. The "temporary acquiring of rhythm in evoked cortical potential" appears when the excitability of the upper brain portion is changed. It then exceeds the optimum of cortical reaction to stimuli. Such an occurrence facilitates the surpassing of the limits of normal functions of the brain, such as cooling (30° to 31° C) or transmission narcoses. When the phenomenon cannot be identified either by the "augmenting" or by the barbiturate vertigo-type of reaction, it is then necessary to take some corresponding measures to evoke reaction of the basic mechanism.

School of Medicine
Charles University
Plzen, Czechoslovakia

2073 Plotnikoff, N., Huang, J., & Havens, P. **Effect of monamine oxidase inhibitors on audiogenic seizures.** *Journal of Pharmaceutical Sciences*, 52(2):172-173, 1963.

Male Swiss mice that are susceptible to audiogenic seizures (21 to 25 days old) and normal albino Swiss mice (25 to 30 days old) were used to test the anticonvulsant effect of the MAO inhibitors iproniazid, tranylcypromine, pheniprazine, etryptamine, phenelzine, and nialamide. In mice that are susceptible to audiogenic seizure, the criterion used to measure protection was the presence or absence of tonic extension. The dose that reduced tonic extension responses to 50% of control values (PD_{50}) was estimated by the technique of Miller and Tainter. The maximal electroshock seizure test was used on normal mice. Tranylcypromine (PD_{50} , 16.5±2.2 mg/kg), pheniprazine (PD_{50} , 11.0±1.6 mg/kg), etryptamine (PD_{50} , 4.1±0.6 mg/kg), phenelzine (PD_{50} , 19.0±3.0 mg/kg), and nialamide (PD_{50} , 8.7±1.1 mg/kg) inhibited the tonic extension component of audiogenic seizures in mice. Iproniazid (PD_{50} , 163±8.5 mg/kg) inhibited both tonic and clonic components. With the exception of etryptamine, all of the inhibitors were inactive in preventing convulsions induced by electroshock.

Stanford Research Institute
Menlo Park, California

074 Erwin, V. G. & Heim, Harold C.
Effects of some hypnotic drugs on respiration and oxidative phosphorylation in rat brain. *Journal of Pharmaceutical Sciences*, 52(8):747-751, 1963.

A series of experiments was performed to determine whether the hypnotic drugs glutethimide, methyprylon, and ethinamate produced effects similar to pentobarbital on respiration and oxidative phosphorylation in brain homogenates and mitochondrial preparations. The brains of young adult, Sprague-Dawley rats of both sexes were used. Experimental methods for each determination are described in detail. Both pentobarbital and glutethimide (10^{-3} M and 5×10^{-4} M) inhibit the endogenous oxygen uptake of homogenates and the oxygen uptake when glucose, pyruvate, malate, or glutamate are added to the homogenates. Neither ethinamate nor methyprylon at these concentrations showed any appreciable effect. Glutethimide and pentobarbital also depress the rate of oxidation of malate, pyruvate, and diphosphopyridine nucleotide in brain mitochondrial preparations. Of the four drugs studied, only pentobarbital evoked significant effects on oxidative phosphorylation by brain mitochondria. None of the drugs produced significant effects on the activity of a purified malic dehydrogenase system.

University of Colorado
Aurora, Colorado

075 Mael, I. H. & Bester, J. F.
Chlorpromazine and dextro-amphetamine as antidotes in acute antihistaminic toxicity in rats. *Journal of Pharmaceutical Sciences*, 52(5):451-453, 1963.

Chlorpromazine and dextroamphetamine were studied in relation to their antidotal effects on antihistaminic toxicity. Toxic doses of diphenhydramine (250 mg/kg) were given by stomach tube to white, adultistar rats. Toxic symptoms elicited were respiratory depression, increased excitation, convulsion, cyanosis, and death. Those animals receiving diphenhydramine and chlorpromazine (10 to 50 mg/kg) showed signs of depression and/or death; those receiving diphenhydramine plus dextroamphetamine (0.15 mg/kg) developed signs of excitation that were more rapid and more severe. The most effective procedure appeared to be the administration of 10 mg/kg

chlorpromazine i.p. as soon as the drug-induced convulsions appeared, and as depression developed, the injection i.p. of dextroamphetamine (0.625 mg/kg). If depression continued or returned, additional doses of dextroamphetamine (0.3 mg/kg) were given. Another experiment using this latter antidotal procedure was set up utilizing 32 additional animals. Similar results were obtained in studies on tripeleennamine toxicity with doses ranging from 100 to 250 mg/kg; antidotal treatment of 4 mg/kg chlorpromazine for each 100 mg/kg histamine and dextroamphetamine 0.25 mg/kg for each 100 mg tripeleennamine was used. Another histamine, thenylpyramine, showed good response, but it required three doses of dextroamphetamine. The same antidotal procedure was used for chlorphenamine toxicity (doses of 10, 15, 20 and 25 mg/kg), and all animals recovered.

University of Southern California
School of Pharmacy
Los Angeles, California

2076 Swinyard, Ewart A., Miyahara, James T., & Goodman, Louis S. Effect of chlorination on the anticonvulsant activity of phenobarbital. *Journal of Pharmaceutical Sciences*, 52(5):463-465, 1963.

The lethal doses, neurotoxic doses, anticonvulsant potencies, and protective indexes were determined in mice for two chlorinated barbiturates, 5-(4-chlorophenyl)-5-ethylbarbituric acid (monochloro) and 5-(3,4-dichlorophenyl)-5-ethylbarbituric acid (dichloro), and the results were compared with similar values determined for the parent compound, phenobarbital. Two tests were used to determine the anticonvulsant potency---the maximal electroshock seizure pattern and the pentylenetetrazol seizure threshold. Chlorination of phenobarbital modified the lethal dose independently of the minimal neurotoxic dose, extended approximately 8-fold the time required for the drug to exhibit peak anticonvulsant activity, and prolonged 3- to 7-fold the time for anticonvulsant activity to fall 50%. The chlorinated barbiturates exhibited anticonvulsant activity by both tests. The monochloro compound was less potent than phenobarbital, but the dichloro compound was of approximately equal potency. The dichloro compound has the most favorable protective index. The protective indexes

for all three compounds were higher on the s.c. pentylenetetrazol test than on the maximal electroshock test.

University of Utah College of Medicine
Salt Lake City, Utah

- 2077 Orzechowski, Raymond F. & Mann, David E., Jr. Effects of *dl*-, *d*-, and *l*-amphetamine on levarterenol tachyphylaxis in the isolated heart of *Venus mercenaria*. Journal of Pharmaceutical Sciences, 52(4):337-340, 1963.

The comparative potencies of *dl*-, *d*-, and *l*-amphetamine in completely blocking the onset of levarterenol tachyphylaxis (characterized by diminished negative inotropic responses) in the isolated heart of the quahog (*Venus mercenaria*) are reported. Pretreatment with the *dl*-isomer (0.80 mg/40 ml sea water), the *d*-isomer (50 mg/40 ml sea water), and the *l*-isomer (0.80 mg/40 ml sea water) indicated that the most potent inhibitor was *d*-amphetamine; *dl*- and *l*-amphetamine were equally active, but were less potent than the *d*-isomer. Observation of positive inotropic responses occurring with higher doses of amphetamine isomers indicated that both the amphetamines and levarterenol may act at the same receptor site. It is also presumed that amphetamine may block the inhibitory sites, thereby allowing levarterenol to exert a stimulatory action.

Temple University
Philadelphia, Pennsylvania

- 2078 Ciuchta, Henry P. & Gautieri, Ronald. Effect of certain drugs on perfused human placenta. III. Sympathomimetics, acetylcholine, and histamine. Journal of Pharmaceutical Sciences, 53(2):184-188, 1963.

In view of the varied results in previous studies of the effects of epinephrine, -epinephrine, levarterenol, and acetylcholine, an investigation was conducted to determine the effects of these agents and to confirm serotonin and histamine activity on isolated vessels of human placentas perfused at

various pressures, and having either long (8 to 10 cm) or short (2 to 3 cm) umbilical cords. Constant perfusion pressures were set between 50 to 90 Hg, and were accompanied by volume inflow rates of 35 to 75 ml per minute. A moderate increase in perfusion pressure was observed in response to 10 μ g to 20 μ g or 200 μ g to 500 μ g of epinephrine and 2 μ g, or 10 μ g to 20 μ g of *l*-epinephrine. Norepinephrine (10 μ g to 20 μ g, 200 μ g to 500 μ g) and acetylcholine (100 μ g) produced only slight increases in perfusion pressure. Histamine (100 μ g, 1,000 μ g) and serotonin (2 μ g to 4 μ g or 50 μ g) caused marked increases in perfusion pressure. The pretreatment with 5 mg of iproniazid did not enhance the action of the sympathomimetic amines significantly, with the exception of histamine. These results indicate that the administration of sympathomimetic amines to vessels of perfused human placentas cause vasoconstriction in almost all preparations with short or long umbilical cords, but to a greater degree in the long cords.

Temple University
School of Pharmacy
Philadelphia, Pennsylvania

- 2079 Piette, Y., Delaunois, A. L., De Schaepdryver, A. F., & Heymans, Imipramine and electroshock threshold. Archives Internationales de Pharmacodynamie et de Therapie, 144(1-2):293-297, 1963.

The effect of imipramine on the electroshock threshold and its possible mechanism of action in this respect were tested in rabbits (1.6 to 2.1 kg in weight). Imipramine (5 mg/kg i.v., 5 minutes before electroshock) was found to provoke a marked increase of electroshock convulsion threshold in rabbits. This increase does not occur in animals given reserpine (1 mg/kg i.v., 24 hours before electroshock), but it is even more marked after pretreatment with iproniazid (100 mg/kg i.p.) and after pretreatment with reserpine (1 mg/kg i.v.) + iproniazid (100 mg/kg i.p.) + *l*-dihydroxyphenylalanine (50 mg/kg i.p.). Depletion of brain noradrenaline stores by α -methyl-*m*-tyrosine (50 mg/kg i.v.) did not impair the imipramine-induced increase in electroshock threshold. These observations indicate that imipramine may induce an increase in electroshock threshold by provoking a sensitization towards dopamine, as previously reported for amphetamine.

University of Ghent
Ghent, Belgium

2080 Boissier, Jacques R. & Dumont, Claude.

Effets spasmodiques du bromure de [methyl-1-pyrrolidino-1)-2-propionyl]-10 phénothiazine (S.D. 104.19) au niveau des organes pelviens. (Spasmodic effects of methyl-1-pyrrolidino-1)-2-propionyl]-10 phénothiazine bromide (S.D. 104.19) in the pelvic organs.) Archives Internationales de Pharmacodynamie et de Therapie, 141(1-2): 1-21, 1963.

Spasmodic effects of [(methyl-1-pyrrolidino-1)-2-propionyl]-10 phénothiazine (S.D. 104.19) on the pelvic region in rats, guinea pigs, rabbits, and dogs were observed. Spasmodic action was observed in vitro on the ureter, bladder, and uterus, and in vivo on the ureter, bladder, uterus, vaginal musculature, and seminal vesicle. Spasmodic action was induced by acetylcholine, barium chloride, serotonin, histamine, adrenaline, and DMPP. Results showed that, in general, S.D. 104.19 (various doses) develops intensive spasmodic action due especially to an acetylcholinolytic action. The drug also showed some antihistaminic and papaverinic activity. Experiments are discussed, and tables accompany the text.

5 rue de l'Ecole de Médecine
Paris, France

2081 Jones, Ann. Ganglionic actions of muscarinic substances. Journal of Pharmacology and Experimental Therapeutics, 141(2):195-205, 1963.

The effects of N-benzyl-3-pyrrolidyl acetate ethobromide (AHR-602), 4-(*m*-chlorophenyl-carbamoyloxy)-2-butyryl-trimethylammonium chloride (McN-A-343), and *DL*-muscarine on the ganglion of a cat were observed. Intrarterial injections of the agents were introduced into the blood supply of the superior cervical ganglion of the cat, and ganglionic effects were measured by contractions of the nictitating membrane. When the ganglion was destroyed, the agents had no effect on the nictitating membrane. They had no effect during depolarizing blockage of the ganglion, but affected the membrane during nondepolarizing blockage of the ganglion. Nicotinic agents with which the three muscarinic agents were compared had no effect during either depolarizing or nonpolarizing blockage. Based on the finding that stimulation of the ganglion is effected by action on a muscarinic receptor that differs from the nicotinic receptor, it is suggested that the attachment of endogenous acetylcholine to

muscarinic receptors at the ganglion cell may serve to modify the normal ganglionic transmission initiated by an action of acetylcholine on the nicotinic receptors.

Harvard Medical School
Boston, Massachusetts

2082 Schmidt, Robert F. Pharmacological studies on the primary afferent depolarization of the toad spinal cord. Pfluegers Archiv für die Gesamte Physiologie des Menschen und der Tiere, 277:325-346, 1963.

The effects of anesthetics, convulsants, and amino acids were tested on the primary afferent depolarization (recorded as dorsal-root potentials and evoked by stimulation of the dorsal or ventral roots) and on the ventral-root reflex responses of isolated hemisectioned spinal cords of the toad *Bufo marinus*. The following compounds were tested: pentobarbital sodium, thiamylal sodium, phenobarbital, chloralose, chloral hydrate, paraldehyde, ether, urethane, strychnine, picrotoxin, GABA, γ -amino-1-propane-sulfonic acid, and glutamic acid. All the anesthetics used decreased the duration of the dorsal-root potentials. The barbiturates and chloralose prolonged the declining phase of the dorsal-root potential in later stages of anesthesia. The ventral-root reflexes were considerably more sensitive to anesthetics than were the dorsal-root potentials. Strychnine did not appreciably affect the amplitude of the dorsal-root potentials. The declining phase, however, was prolonged and showed "humps" in the later stages of strychnine poisoning. Picrotoxin reduced the size of the dorsal-root potentials with or without a slight prolongation of the declining phase. The GABA, γ -amino-propane-sulfonic acid, and glutamic acid reduced the size of the dorsal-root potential. Testing the excitability of dorsal-root fibers showed that GABA and γ -amino-propane-sulfonic acid had a slight depolarizing effect, whereas glutamic acid considerably depolarized the dorsal-root fibers. The results obtained in this study were compared with the results of similar tests on the spinal cord of the cat. It was postulated that in both species, primary afferent depolarization is produced by a similar mechanism. The mode of action of the anesthetics and convulsants and the possible role of the amino acids as transmitter substances in the pathway of primary afferent depolarization are discussed.

Australian National University
Canberra, Australia

- 2083 Dravid, A. R., Di Perri, Raoul, Morillo, A., & Himwich, H. E. Alcohol and evoked potentials in the cat. *Nature*, 200(4913):1328-1329, 1963.

The results of the effects of alcohol on the evoked responses recorded from the reticular formation and cortex, following stimulation of the sciatic nerve, are presented. Fourteen intact adult cats were tracheotomized and both femoral veins and one femoral artery were cannulated. Concentric needles and recording electrodes were located on the somatosensory cortex. The central stump of the cut sciatic nerve (contralateral to the recording electrodes) was electrically stimulated (7 to 9 volts and 0.1 to 0.2 milliseconds in duration every 2 seconds). Ethyl alcohol (20% solution at 1 g/kg) was injected into one of the femoral cannulas for 2 to 3 minutes. Two minutes after alcohol administration, the response from the somatosensory cortex was markedly depressed, while the reticular response was partially depressed. Recovery, to some extent, was observed 1 hour after alcohol treatment, although the recovery of cortical response was retarded, in comparison with that of the reticular formation. There was a moderate drop in blood pressure of about 15 to 20 mm mercury, but the blood pressure values recuperated in about 5 to 15 minutes after alcohol injection. In the reticular formation and the somatosensory cortex, the blood-alcohol levels increased from 8 mg percent to 123 mg percent. These results indicate that the cortex is affected more by ethanol than is the reticular formation.

Galesburg State Research Hospital
Galesburg, Illinois

- 2084 McGrath, W. R. & Ketteler, H. J. Potentiation of the anti-reserpine effects of dihydroxyphenylalanine by antidepressants and stimulants. *Nature*, 199(4896):917-918, 1963.

In these experiments on the potentiation of the antireserpine effects of dihydroxyphenylalanine by antidepressants and stimulants, female albino mice (18 to 24 g in weight) were used. Reserpine (10 mg/kg i.p.) was administered, and 3 hours later, *DL*-DOPA was administered; the ED_{50} was found to be 520 mg/kg. In eight animals, nialamide (ED_{50} = 3.7 mg/kg i.p.) amitriptyline (ED_{50} = 3.7 mg/kg i.p.), imipramine (ED_{50} = 5.0 mg/kg i.p.) and

D-amphetamine (ED_{50} = 0.55 mg/kg i.p.) were given 2 hours after 10 mg/kg reserpine and 1 hour after the test drug *DL*-DOPA (520 mg/kg) was given. The arousal induced by the test drug plus DOPA was similar to that caused by higher doses of DOPA alone (1,080 mg/kg). The psychomotor stimulant *D*-amphetamine was more potent than were the antidepressants. The effect of nialamide was probably due to its anti-MAO activity, whereas the results with imipramine and amitriptyline reinforce the idea that many of the activities of the MAO inhibitors are possessed by substances that do not inhibit the enzyme.

Wm. S. Merrell Co.
Division of Richardson-Merrell Inc.
Cincinnati, Ohio

- 2085 Curtis, D. R. & Ryall, R. W. Central actions of psychotomimetics. *Nature*, 199(4897):1003-1004, 1963.

The actions of *N*-ethyl-3-piperidyl α,α -diphenylacetate, and *N*-methyl-3-piperidyl α,α -diphenylglycolate methochloride and of the psychotomimetics *N*-methyl-3-piperidyl α,α -diphenylglycolate and *N*-ethyl-2-pyrrolidylmethyl α -cyclopentyl- α -phenylglycolate were measured on the extracellular spike potentials of single neurones in the spinal cord and thalamus of cats anesthetized with pentobarbital sodium. The glycolic acid esters were ejected electrophoretically. Results showed that these substances reduced the excitability of central neurones and antagonized the action of acetylcholine on cholinceptive neurones. Three possible mechanisms by which these substances may produce alterations in human behavior and mental activity when they reach central neurones are presented.

Australian National University
Canberra, Australia

- 2086 Cervoni, Peter, Bertino, Joseph, & Geiger, Leslie E. Medullary vagal effects of *D*-lysergic acid diethylamide in the decerebrate cat. *Nature*, 199(4894):700-701, 1963.

The medullary vagal effects of *D*-lysergic acid diethylamide (LSD-25) and 2-bromo-*D*-lysergic acid (BOL-148) have been studied

the decerebrate cat. In 20 cats (2 to 4 in weight) LSD-25 (0.2, 0.3, 0.4 mg/kg i.v.) produced bradycardia, hypotension, and a decrease in respiratory rate. The BOL-148 (0.4 mg/kg i.v.) produced mild transient slowing of the heart and mild hypotension lasting not more than 60 seconds, whereas the effects of 1 and 2 mg/kg were more pronounced and lasted 3 to 5 minutes. The LSD-25 appeared to have a dullary stimulating action, but BOL-148 probably has direct cardiac toxicity in large doses.

Experimental Medicine and Neuropharmacology Branch
U.S. Army Chemical Warfare Laboratories
Navy Chemical Center, Maryland

37 Marley, E. & Vane, J. R. **Tryptamine receptors in the central nervous system: Effects of anaesthetics.** *Nature*, 1963, 198(4879):441-444.

The effects of various anesthetics were studied on the tryptamine receptors in the brain of cats; both normal cats and spinal cat preparations were used. Anesthesia was induced with ethyl chloride and ether. Anesthesia was then maintained with chloralose (0.5 mg/kg i.v.), hydroxydione (70 mg/kg i.v.), halothane and oxygen, or pentobarbital sodium (20 or 35 mg/kg i.v.). In some cases, anesthesia was induced with pentobarbital (35 mg/kg i.p.). Preparations for mechanical and electrical recording are described. With anesthetic doses of chloralose and hydroxydione, there was minimal depression of the spinal reflexes and of the facilitatory effects of tryptamine. With halothane anesthesia, the depression of the reflexes was greater, but the tyramine effects could still be elicited. When halothane plus chloralose or hydroxydione was given, the knee jerk and the polysynaptic reflex disappeared; tryptamine still produced a rise in basal tone and partially restored the reflex. In contrast, direct depressant action of pentobarbital on the spinal cord, and the action mediated through the reticular formation makes it an unsatisfactory anesthetic for investigating, not only normal reflex functions, but also the effects of drugs on them.

St. Mary's Hospital
London SE.5, England

2088 German, G. A. & Kemali, D. **Physiology. Effect of extracts from the urine of schizophrenic patients on the evoked cortical response in the rat.** *Nature*, 1963, 198(4882):791-792.

Local application of urinary fractions from 24-hour urine specimens of six schizophrenic patients, who had received no drugs 4 weeks prior to the collection of the urine, was used to study the action on evoked cortical responses. The sera of these schizophrenics had previously produced a marked increase in the amplitude of cortical evoked responses following local cortical application. Urinary fractions from five healthy control subjects were also studied. Fifteen responses were photographed every 5 minutes for a period of 10 minutes before and 40 minutes after application of the urinary fraction solution to the cortex of anesthetized rats. Urinary fractions from schizophrenic patients were found to enhance the amplitude of the evoked responses with a continuing increase up to 40 minutes, whereas the evoked response in the controls did not reveal a marked increase, and the maximum amplitude was achieved in 10 to 15 minutes. The results from the urinary fractions of schizophrenics were identical to those using sera from schizophrenics.

University of Naples
Naples, Italy

2089 Philippu, A. & Schümann, H. J. **Effect of ribonuclease on the ribonucleic acid, adenosine triphosphate and catecholamine content of medullary granules.** *Nature*, 1963, 198(4882):795-796.

The ribonucleic acid content of chromaffin granules and its relationship to ATP and catecholamine content, and the influence of ribonuclease on ribonucleic acid, the catecholamines, and ATP are described. Chromaffin granules were prepared from suprarenal medulla of cattle. One mg of the granules contained 31.3 µg ribonucleic acid, 167.8 µg catecholamines, and 80.4 µg ATP. Incubation of the granules at 37° C for 30, 60, and 120 minutes showed that the spontaneous release of catecholamines and ATP is accompanied by an equivalent loss of ribonucleic acid. The addition of 66 µg to 1,800 µg ribonuclease produced an increased and dose-dependent release of all three substances to the same percentage extent.

Inactivated ribonuclease neither depolymerizes ribonucleic acid nor releases catecholamines and ATP. At 0° C, no spontaneous release of the three substances occurs. These observations favor the hypotheses that ribonucleic acid is involved in the storage of ATP and the catecholamines in medullary granules, and that an intragranular ribonuclease is responsible for the spontaneous release of these three substances.

University of Frankfurt
Frankfurt, Germany

- 2090 Abood, L. G., Koyama, I., & Kimizuka, H. A possible mechanism of action of calcium and some psychotomimetic agents on membranes. *Nature*, 197(4865):367-368, 1963.

Studies are reported on the possible mechanism of action of calcium ions and the psychotomimetic agent *N*-methyl-2-pyrrolidyl methyl cyclopentylphenyl glycolate (PMCG), on biological membranes. Experiments on resting potentials in frog sartorius muscles are described. A pair of muscles was soaked in Ringer's solution for 30 minutes before the resting potentials of each muscle were determined. One muscle was then transferred to calcium-free Ringer's solution, one was transferred to calcium-free Ringer's solution containing 10^{-4} M PMCG, and the resting potentials were determined after 40 minutes. Experiments were also performed with calcium-free Ringer's solution containing 4 mM EDTA. In calcium-free solutions, the resting potential drops rapidly. The PMCG (10^{-4} M) restores the potential to normal. Similarities in the actions of calcium and PMCG are described. It was concluded that the actions of calcium and PMCG in these preparations were surface phenomena. Studies of the action of calcium and PMCG on the physical properties of interfacial films are then discussed.

University of Illinois College of Medicine
Chicago, Illinois

- 2091 Williams, R. B., Humphries, W. R., & Mills, C. F. Influence of phenothiazine administration on cytochrome oxidase activity in lamb brain tissue. *Nature*, 198(4878):387-388, 1963.

Twenty Scottish Blackface ewes were treated with 10-g doses of phenothiazine at 8 and 6

weeks before lambing in order to determine the influence of this drug on cytochrome oxidase activity in the lamb brain. Five lambs were killed at 6 weeks of age (Group B); 4 lambs of the same age were killed 36 hours after administration of 5 g of phenothiazine (Group C); and 5 lambs of the same age used as controls were from ewes who had not received the drug (Group A). There was reduced cytochrome oxidase activity in Groups B and C following phenothiazine administration. The copper concentration of brain tissue was not influenced by the phenothiazine treatment, and was well above the level found to be associated with swayback. It is suggested that phenothiazine administration to copper-deficient animals may lower an already depressed cytochrome oxidase. In view of this, caution should be used in the use of phenothiazine and its derivatives during pregnancy and also in the young lamb where copper deficiency may exist, especially where swayback outbreaks have occurred.

Rowett Research Institute
Buckburn, Aberdeen

- 2092 Tauc, L. & Bruner, J. 'Desensitization' of cholinergic receptors by acetylcholine in molluscan central neurones. *Nature*, 198(4875):33-35, 1963.

Experiments were performed on ganglion cells from the mollusks *Aplysia depilans* and *Archachatina marginata* to determine whether the process of desensitization to acetylcholine, described for the motor end plate also occurs in these central neurons. The results are summarized as follows: (1) During continuous local ionophoretic injection of acetylcholine on the somatic membrane, the amplitude of initially produced depolarization in D-cells (hyperpolarization in H-cells) usually decreases with time. (2) The efficacy of acetylcholine in modifying the polarization of the membrane decreases when the drug is repeatedly applied to the membrane at short intervals. (3) The transient depolarization produced by repeated applications of identical doses of acetylcholine (test pulse) progressively decreases during simultaneous application of a continuous dose of acetylcholine (conditioning pulse) with another electrode. (4) The susceptibility to desensitization and the rate of recovery of a given cell seem to be identical all over the surface of the somatic membrane. (5) The kinetics of

sensitization is similar in D- and H-
 11s. (6) The desensitization is limited
 the region reached by the conditioning
 lse. (7) Impedance measurements showed
 at the process of desensitization is not
 lated to variations of the membrane im-
 dence. (8) Similar kinetics of desensiti-
 tion were observed when acetylcholine was
 placed by carbachol.

Centre National de la Recherche Scientifique
 Paris, France

2093 Hall, W. J. & Sheehan, J. D. Release
 of catecholamines from the atrium of
 the dog by tyramine. *Nature*, 197(4872):
 1116-1117, 1963.

method is described for demonstrating the
 release of vasoactive material from the
 atrium of the dog by tyramine. The vaso-
 active material was thought to be a
 catecholamine because of the response of the
 aortic strip. Cyproheptadine (an anti-
 histamine and an anti-5HT agent) decreased
 the response of the aortic strip to added
 tyramine and abolished the response to added
 histamine, but there was no change in the
 response to added noradrenaline or to the
 vasoactive material.

University College
 Department of Physiology
 Cork, Ireland

2094 Pfeiffer, Carl J., Gass, George H.,
 & Schwartz, Clyde S. Reduction by
 chlorpromazine of ulcers due to acute star-
 vation in mice. *Nature*, 197(4871):1004-
 1015, 1963.

This investigation was undertaken to estab-
 lish whether the tranquilizer chlorpromazine
 could prevent or decrease the incidence in
 mice of acute gastric ulceration caused by
 starvation. Adult Swiss mice (121 males and
 79 females) were fasted for 3 days and in-
 jected s.c. with chlorpromazine b.i.d. (10
 mg/kg for the initial injection and 5 mg/kg
 for each of the remaining five injections)
 and were injected similarly with water. At
 the end of the third day, the mice were
 killed with chloroform and were autopsied
 immediately. The occurrence of ulcers in
 the female experimental mice was compared

with that of the starved female water-con-
 trol mice and also with 50 normal male and
 50 normal female mice. The data on starved
 male mice were not included because of a
 very high mortality rate (65%). A signifi-
 cant reduction of gastric ulcers occurred in
 mice treated with chlorpromazine (17.2% had
 ulcers) as compared with the water-control
 mice (29.4% had ulcers). Lethargy, de-
 creased motor activity, and a decrease in
 postural muscle tone was observed in the
 chlorpromazine-treated animals. It is con-
 cluded that chlorpromazine may have reduced
 the incidence of ulceration by means of its
 inhibition of gastric-acid secretion.

Southern Illinois University
 Carbondale, Illinois

2095 Simon, Eric J. Inhibition of
 synthesis of RNA in *E. coli* by the
 narcotic drug laevorphanol. *Nature*,
 198(4882):794-795, 1963.

The inhibition of the synthesis of RNA in
E. coli by the morphine analog levorphanol
 has been demonstrated by the measurement of
 the incorporation of phosphate-32 into RNA
 nucleotides and of tritiated thymidine into
 the acid-insoluble fraction in the same
 levorphanol-inhibited culture. Incorpora-
 tion of the phosphate-32 into RNA was re-
 duced by a factor of 6 to 10 over that in
 control cultures, whereas, there was little
 effect on the synthesis of DNA. Since the
 drug has shown little effect on the forma-
 tion of acid-soluble nucleotides, and uracil
 or rich culture media fail to protect, it
 seems unlikely that the inhibitory effect
 is on the formation of RNA precursors.

New York University School of Medicine
 New York 16, New York

2096 Sackler, A. M., Weltman, A. S., &
 Owens, H. Effects of lysergic acid
 diethylamide on urinary 17-ketosteroid and
 17-OH corticosteroid levels of female rats.
Nature, 198(4885):1119-1120, 1963.

The effects of prolonged and intermittent
 administration of LSD-25 on adrenal function
 were determined by evaluating alterations in
 urinary 17-ketosteroid and 17-hydroxycorti-
 costeroid levels. The subjects, 48 female

Wistar rats, weighing 100 g, were divided equally into three groups. Group A and B rats were injected s.c. with 50 μ g and 75 μ g doses of LSD-25 dissolved in normal saline. Group C controls received an equivalent 1 ml volume of saline. Six injections were administered on alternate days. The results indicated that the higher dose of LSD-25 produced greater alterations in steroid levels, but the differences between Groups A and B were not statistically significant. Since LSD-25 induced pronounced increases in 17-hydroxycorticosteroid levels and moderate increases in 17-ketosteroid levels, increased pituitary-adrenocortical activity in the female rats is suggested. The findings of a stimulatory effect on the pituitary-adrenal system parallel conditions noted in certain schizophrenias.

Brooklyn College of Pharmacy
Long Island University
Brooklyn, New York

- 2097 Sankar, D. V. Siva, Broer, Henry H., & Gates, Norman. **Histamine-binding action of lysergic acid diethylamide.** *Nature*, 200(4906):582-583, 1963.

It has been reported previously that LSD-25 increases the levels and binding of serotonin, as well as inhibits or reduces anaphylactic shock in guinea pigs. In view of the involvement of serotonin and histamine in anaphylactic shock, the effect of LSD-25 on the levels of free and bound histamine was investigated. Adult, male, albino rabbits were given 20 μ c of histidine-2-C¹⁴, and 90 minutes later, they received i.v. injections of LSD-25 (500 μ g). The total level of histamine decreased, whereas, the bound form of histamine (mitochondrial sediment) increased.

Creedmoor State Hospital
Jamaica 27, New York

- 2098 Gerson, T. & Shorland, F. B. **Effect of β -sitosterol on cholesterol and lipid metabolism in the rat.** *Nature*, 200(4906):579-580, 1963.

The actual cells involved in the previously reported acetylcholine excitation of elements in the cerebellar cortex have been

identified. The vermis cerebelli of cats anesthetized with pentobarbital sodium (35 to 40 mg/kg i.p.), in which acetylcholine was applied electrophoretically, were used. The neurones were identified as Purkinje cells by the following criteria: depth beneath the cortical surface, antidromic response to stimulation near the fastigial nucleus by means of a stereotactically placed concentric electrode, and the response to local stimulation of parallel fibers at a point 0.5 to 1.0 mm along the same folium from the site of recording. Carbaminocholine was found to be a considerably more potent and prolonged excitant of Purkinje cells than was acetylcholine. The findings presented here indicate that the acetylcholine-sensitive receptors of Purkinje cells differ from those of Renshaw cells, and this may, in part, explain the difference in time parameters of the acetylcholine excitation.

Australian National University
Canberra, Australia

- 2099 McLean, J. R. & Chen, G. **Elevation by propynylamines of rat tissue norepinephrine-levels and reserpine antagonism in mice.** *Nature*, 200(4907):686, 1963.

The elevation by the hydrochlorides of 2-propynylamine, di-2-propynylamine, and tri-2-propynylamine of rat tissue norepinephrine levels and reserpine antagonism in mice was investigated. The heart and brain norepinephrine levels of five rats, injected i.p. with 2-propynylamine HCl (10 mg/kg/day and 40 mg/kg/day) for 4 days, were elevated to 151% and 122% for the lower dose and 30% and 85% for the higher dose. At 50 mg/kg i.p., 2-propynylamine HCl produced anti-reserpine activity for 9 days in mice treated with 4 mg/kg of reserpine and an 0.5% solution of pentylenetetrazol. The hydrochlorides of di-2-propynylamine and tri-2-propynylamine also possessed anti-reserpine activity but were less active than 2-propynylamine HCl.

Parke, Davis, and Company
Research Laboratories
Ann Arbor, Michigan

- 2100 Green, J. P., Carlini, E. A., & Robinson, J. D. **Acetylcholine-releasing material in neural tissues.** *Nature*, 200(4911):1108-1109, 1963.

From the examination of cholinergic substances in the sciatic nerve, it was

erved that acetone and lipid extracts of sciatic nerve of a rabbit caused a slow retraction of the guinea pig ileum. Failure of the lipoidal material to act on the ileum or anoxic ileum, and the sensitivity of the activity to atropine suggested that the substance may act by releasing acetylcholine from the nerve plexus in the wall of the ileum. Investigations with a hemicholinium, which prevented the synthesis of acetylcholine and the action of the extract on the ileum, strengthened this view. None of the catecholamine inhibitors (LSD, 0.005 µg/ml, mepyramine, 0.005 µg/ml, atropine, 0.006 µg/ml, hexamethonium, 20.0 µg/ml, tetraethylammonium, 40.0 µg/ml, and cocaine, 0.001 µg/ml) affected the action of the extract, whereas morphine (0.001 µg/ml) completely blocked the action.

University School of Medicine
Haven, Connecticut

Pettinger, William, Horwitz, David, Spector, Sydney, & Sjoerdsma, Albert. **Enhancement by methyl dopa of tyramine sensitivity in man.** *Nature*, 200(4911):1107-1108, 1963.

amine sensitivity in man was determined by 15-minute infusions of tyramine in hypertensive patients under three different conditions: (1) during control conditions; (2) after 4 to 20 weeks of oral treatment with 2 to 3 g/day of methyl dopa; (3) during the last 3 days of treatment with reserpine (1 to 2 mg/day i.m.) for 8 weeks. Pressor responses to tyramine were enhanced by methyl dopa, whereas reserpine decreased tyramine pressor activity. Tyramine sensitivity was increased when three patients receiving reserpine (1 to 2 mg/day) for 11 days were given methyl dopa (2.0 g p.o.) for the last 3 days. These results indicate that the clinical hypotensive response of methyl dopa bears a close relationship to the magnitude of tyramine response than to any other parame-

onal Heart Institute
esda, Maryland

Pepeu, Giancarlo. **Effect of 'Tremorine' and some anti-Parkinson's disease drugs on acetylcholine in the rat's brain.** *Nature*, 200(4909):895-896, 1963.

effects of tremorine (1,4-dipyrroli-2-butylene) and some antiparkinsonian

drugs on the brain acetylcholine of adult, male rats (150 to 200 g) were investigated. The rats, injected with the drugs (0.1 to 0.4 ml i.p.), were decapitated, and the brain acetylcholine was extracted and estimated on the isolated eserinizated rectus abdominis muscle of the frog. Tremorine (30 mg/kg) alone induced an increase of the total brain acetylcholine, which closely followed the onset of the tremor. Pretreatment with atropine sulfate (5 and 30 mg/kg) or caramiphen HCl (20 and 30 mg/kg) prevented tremor, rigidity, and parasympathetic stimulation, and also decreased brain acetylcholine. Diethazine (antiparkinsonian drug) at 30 and 40 mg/kg prevented the onset of tremorine symptoms but only diminished the acetylcholine. No definite evidence that the increase of brain acetylcholine is responsible for the tremorine-induced symptoms was found.

University of Pisa
Pisa, Italy

2103 Desmedt, J. E. & Delwaide, P. J. **Neural inhibition in a bird: Effect of strychnine and picrotoxin.** *Nature*, 200(4906):583-585, 1963.

The influence of strychnine and picrotoxin on the inhibition produced by the efferent cochlear bundle was studied in adult pigeons. The spinal cord was transected at the C3 level. Spontaneous electrical activity of the brain and spinal cord and ECG's were measured. Auditory responses evoked by a click or tone pip delivered to the auditory meatus were measured at the round window. Strychnine sulfate (2 to 3 mg/kg i.v.) quickly eliminated the efferent inhibition without changing the control response evoked by the testing click. Picrotoxin did not antagonize inhibition even when administered in convulsant doses. Species differences in the response to strychnine and picrotoxin in the cat and pigeon are described. Strychnine convulsions in the pigeon seem to depend on the removal of inhibitory processes in the spinal cord.

University of Brussels
Brussels, Belgium

2104 Crawford, J. M., Curtis, D. R., Voorhoeve, P. E., & Wilson, V. J. **Strychnine-resistant central inhibition.** *Nature*, 200(4909):843-846, 1963.

Three examples are given of postsynaptic inhibition in areas of the brain that is resistant to the depressant action of

strychnine, even when the drug is given in doses that virtually eliminate postsynaptic inhibition in the spinal cord. Adult cats were anesthetized with pentobarbital sodium. Intracellular recordings were made by glass microelectrodes filled with 3 M potassium chloride or 2 M potassium citrate; extracellular recordings were made with microelectrodes filled with 4 M sodium chloride. Recordings were made on the pyramidal cells of the hippocampus, the Purkinje cells of the cerebellum, and the ventrobasal cells of the thalamus. The powerful inhibitory action on each of these cells was resistant to doses of strychnine up to 0.9 mg/kg i.v. Two possible explanations are given for the failure of strychnine to exert its depressant effect: (1) The transmitters responsible for the inhibition are different in the brain and in the spinal cord. (2) The transmitters may be the same, but the receptors may differ.

(No address)

- 2105 Quinton, R. M. & Halliwell, G.
Effects of α -methyl DOPA and DOPA on the amphetamine excitatory response in reserpinized rats. *Nature*, 200(4902):178-179, 1963.

The effects of DOPA and α -methyldopa on the amphetamine-induced excitatory response was studied in reserpinized male, albino Wistar rats (160 to 240 g in weight). Doses of 5 mg/kg amphetamine sulfate i.p. caused a moderate excitatory response in rats; treatment with methyldopa (400 mg/kg i.p.) 2 to 3 hours before amphetamine reduced the response. In reserpinized animals (2.5 mg/kg reserpine i.p. 18 hours before amphetamine), the excitatory response was markedly accentuated. If methyldopa was given just before reserpine, the amphetamine response was like that in normal animals. If methyldopa was given 2 hours before amphetamine in reserpinized rats, excitation was abolished. The blockade of the amphetamine response by reserpine and methyldopa was reversed by 20 to 50 mg/kg DOPA s.c. 0.5 to 1.5 hours after amphetamine. The blocking effect of reserpine and methyldopa was not seen in rats given 100 mg/kg nialamide or 5 mg/kg tranlycypromine 1.5 to 9 hours after reserpine. Dopamine (100 mg/kg) and 5HT (50 mg/kg) did not induce reversal of the blocking effect. The blockade of amphetamine excitation by reserpine and methyldopa

may arise from a summation of their effects in depleting the brain of active amines. The role of DOPA in the reversal of the blockade is discussed.

Pfizer Ltd.
Sandwich, Kent, England

- 2106 Baker, J. C. & Enoch, M. David.
Combining the antidepressant drugs. *Lancet*, 2:943, 1963. (Letter).

A warning against the combined use of antidepressant drugs, especially the use of drugs with MAO inhibitors, is reiterated in reply to a comment (October 12 issue) on a previous warning. Administering a specific antidepressant drug for a specific syndrome cluster is preferable to combined therapy. The deleterious side effects that can occur with prolonged drug therapy, particularly with the phenothiazines, are also stressed.

Shelton Hospital
Shrewsbury, England

- 2107 Safir, Aran. Effect of topically administered drugs on retinal directional sensitivity. *Journal of the Optical Society of America*, 53:1007-1008, 1963. (Letter).

Calculation of the variations of α (a measure of the magnitude of the Stiles-Crawford effect) brought about by the instillation of drugs in the conjunctival sac may be done by employing $\log \eta = -\alpha r^2$, where η = the ratio of the light brightness seen entering through peripheral as compared to central pupil position; and r = the distance in ml's of the peripheral entry point from the pupil brightness center. A brightness match was made each 30 seconds for 20 minutes, after which amphetamine sulfate 2% was instilled into the conjunctival sac. Brightness matches were then made at 30-second intervals for 5 minutes, alternating with 5 minutes of rest. A similar procedure was followed to test the effect of homatropine. No change in either the directional sensitivity or in the orientation of the retinal receptors was observed.

Albert Einstein College of Medicine
New York, New York

See also: 1883, 1886, 1887, 1922, 1945, 1965, 1982, 1992, 2014, 2020, 2023, 2110, 2112, 2113, 2122, 2124, 2132, 2133

BIOCHEMISTRY

8 Kalbhen, D. A. & Sargent, T. W.
Preliminary studies of the distribution and fate of ^{82}Br -labelled 2-brom-D-lysergic acid diethylamide (BOL) in the human body. *Medicina Experimentalis*, 200-208, 1963.

Studies of the distribution of Br^{82} -labeled brom-D-lysergic acid diethylamide (Br^{82} -BOL) were carried out in order to elucidate the distribution and fate of LSD-25, since there are no great differences between the distribution of LSD and brom-LSD in the human body. The factors governing passage of the drugs across the body membranes are the same. Three normal, white males (28, 34 and 34 years old, respectively) and weighing 166, 177, and 145 pounds, respectively, were given 20 μC of bromide ^{82}Br -LSD. The Br^{82} activity, as measured by a multiple port counter, showed an initial accumulation in the liver (10 minutes after injection) and a later accumulation in the upper abdomen, but there was no marked accumulation of tracer in other organs. No activity was seen in the lung. The Br^{82} activity in the plasma and in formed elements of the blood showed a steady increase to 9 hours and then remained constant for 48 hours. Formed elements contained as much activity as plasma. Radioactivity was excreted relatively slowly, the whole body count falling to 50% of the injected dose in 6 days. Even though the Br^{82} activity was initially highly concentrated in the intestinal tract, the average excretion in the stool was only 9% of the urinary excretion.

University of California
Berkeley, California

9 Kalbhen, D. A. The microsynthesis of ^{82}Br -labelled 2-brom-D-lysergic acid diethylamide (BOL). *Medicina Experimentalis*, 9:20-24, 1963.

Technique for synthesizing small amounts of Br^{82} -labeled BOL is described. Bromination was accomplished with molecular bromine. Reaction products were separated

by thin-layer chromatography. The estimation of the amount of BOL was done spectrophotometrically, and the radioactivity was measured in the whole body counter.

University of California
Berkeley, California

2110 Nieforth, Karl A. 2-Aminobenzenethiol derivatives as potential psychotherapeutic agents. *Journal of Pharmaceutical Sciences*, 52(12):1136-1139, 1963.

A structural similarity between reserpine and chlorpromazine has been found, and a group of 2-aminobenzenethiol derivatives, designed to match the similarity, has been synthesized. The similarity is the proximity in space occupied by substituents on position 2 of chlorpromazine and position 16 of reserpine. It appears that the two sites involved in CNS activity may be closely related in physical characteristics or that only one site may be involved. The 2-aminobenzenethiols were designed to have a hybrid reserpine--chlorpromazine activity. Activity of this type would suggest the existence of a single site with differences that are observed in the pharmacodynamic actions accounted for by secondary effects of the drugs.

University of Connecticut
Storrs, Connecticut

2111 Graham, Horace D., Baker, Yede Marie., & Njoku-Obi, A. N. Complex formation between hydrocolloids and tranquilizers and hypotensive agents. *Journal of Pharmaceutical Sciences*, 52(2):192-198, 1963.

A study is reported of the interactions of four groups of hydrocolloids---sulfated, carboxylic acid type and neutral polysaccharides, proteins, and other

compounds---with tranquilizers (promazine and chlorpromazine 0.5% in distilled water) and hypotensive agents (reserpine 0.1% in distilled water, veriloid 0.1% in dilute acetic acid, veratrine sulfate 0.5% in distilled water, and veratrine alkaloid 0.1% in dilute acetic acid). The sulfated polysaccharides were the most reactive hydrocolloids. Of the several variables that affect the interaction of promazine with carrageenan (Seakem type 5), the pH of the interaction medium is the most important. Maximum interaction occurs at 45° C and at a pH of 4.95. Meprobamate and hexamethonium chloride form much weaker complexes, as evidenced by their failure to produce turbidity with several hydrocolloids tested. Solubility of the promazine hydrochloride--carrageenan complex in sodium chloride and hydrochloric acid showed the order of tolerance of the added salts to be monovalent, divalent, and trivalent. The trivalent cations will precipitate carrageenan and other hydrocolloids at low concentrations. Promazine hydrochloride complexes of carrageenan (Seakem type 5) and sodium carboxymethylcellulose are highly insoluble in sodium chloride and hydrochloric acid. After intramuscular injection of the carrageenan--promazine hydrochloride complex into rabbits, free promazine was detected in the blood up to 6 days after administration, as contrasted to the disappearance of the free form after only 24 hours.

The George Washington Carver Foundation
Tuskegee Institute
Tuskegee, Alabama

2112 Whittle, Charles W. & Castle, Raymond N. Open-chain analogs of LSD II, synthesis of some 2-(3-indolyethyl)- and 2-(3-methyl-2-indolyethyl) piperidines. *Journal of Pharmaceutical Sciences*, 52(4): 645-648, 1963.

The synthesis of some 2-(3-methyl-2-indolyethyl) piperidines, analogs of LSD, is discussed. The results of the pharmacological screening have not been given due to their lack of interesting activity.

Georgia State College
Atlanta, Georgia

2113 Poole, John W. & Gardocki, Joseph F. Prolongation of chlorzoxazone plasma levels by zoxazolamine. *Journal of Pharmaceutical Sciences*, 52(5):486-489, 1963.

The absorption patterns of chlorzoxazone (5-chlorobenzoxazolinone) when administered

alone and in combination with zoxazolamine were studied in mice, dogs, and human beings. Possible mechanisms responsible for the prolongation of chlorzoxazone plasma level when administered with zoxazolamine are discussed. Methods for determining chlorzoxazone and zoxazolamine levels are presented. Chlorzoxazone plasma levels were determined in 10 human subjects who received 0.50 g p.o.; in 12 dogs divided into two groups, which received either 30 mg/kg or 60 mg/kg; and in mice receiving 100 mg and 200 mg/kg i.p. The mean plasma levels were also obtained in mice and dogs receiving chlorzoxazone and zoxazolamine (100 mg/kg each for mice and 60 mg/kg each for dogs). In both mice and dogs, there was a significant prolongation of the chlorzoxazone plasma concentration when given in conjunction with zoxazolamine. Zoxazolamine was also given alone to mice and dogs (100 mg and 60 mg/kg, respectively); the early levels noted in both species were lower when the combination of drugs was administered than when zoxazolamine was given alone. Brain homogenates of mice that had been given 2 mg/kg of chlorzoxazone alone and 200 mg/kg in combination with 50 mg/kg zoxazolamine indicated that the brain levels are proportional to the plasma levels of chlorzoxazone. Brain levels of zoxazolamine (50 mg/kg) in combination with chlorzoxazone (200 mg/kg) showed the levels to be lower in the combined-drug treated mice than in those treated with zoxazolamine alone.

McNeil Laboratories, Inc.
Fort Washington, Pennsylvania

2114 Higuchi, W. I. & Hamlin, W. E. Release of drug from a self-coating surface, benzphetamine pamoate pellet. *Journal of Pharmaceutical Sciences*, 52(6): 575-579, 1963.

The results are presented of a detailed mathematical analysis of the problem in which the rate of release of benzphetamine from pellets of benzphetamine pamoate in 0.12 N hydrochloric acid medium is controlled by a coat, which is formed by precipitation of pamoic acid onto the pellet surface. A series of experiments, using hanging pellet method, at 0.12, 0.06, and 0.012 N hydrochloric acid were carried out. When the theory was applied to the data, appeared that the disagreement exists largely on time dependence, not on the coefficient or the hydrogen ion concentration.

School of Pharmacy
University of Michigan
Ann Arbor, Michigan

5 Rosen, Earl. Relationship of in vitro release to urinary recovery in of a sustained-release preparation of prochlorperazine. *Journal of Pharmaceutical Sciences*, 52(11):98-100, 1963.

sustained-release preparation of S^{35} -labeled prochlorperazine prepared with three different in vitro release patterns, as determined by the rotating-bottle method, given to 16 human subjects to determine whether a relation exists between in vitro release measurements and human in vivo response. Twenty-three observations were made, with 7 of the 16 subjects receiving the second formulation 2 weeks after the first. Seven subjects received the fast formulation, nine received the normal, and seven received the slow. Urine was collected 12 hours after drug administration, and recovery of S^{35} was determined by liquid scintillation counting. Previously published data on sustained-release preparations of propylpropanolamine and trimiprazine, reported in the same fashion as the prochlorperazine data, are included. For each specific dosage form of each drug, a direct rank relationship was found to exist between in vitro data and the respective in vivo data.

Smith, Kline and French Laboratories
Philadelphia, Pennsylvania

6 Moody, Joseph E., Jr. Determination of amphetamine in dosage forms by thin layer chromatography. *Journal of Pharmaceutical Sciences*, 52(8):791-793, 1963.

A method is presented for the assaying of small samples of amphetamine and several sympathomimetic amines. The extraction of amphetamine from the dosage form is achieved by elution from an immobile aqueous phase of a column with a solution of triethylamine in chloroform. The eluate is quantitatively determined by ultraviolet absorption of the acid solution. Results obtained on 11 samples of 5 mg dextro-amphetamine tablets assayed by three different methods—the U.S.P. XVI procedure, distillation-ultraviolet absorption procedure, and the column-ultraviolet procedure described in this paper—favor the column-ultraviolet absorption method as the simpler and more rapid method of assay. The U.S.P. XVI procedure was shown to have several undesirable aspects.

Food and Drug Administration
Washington, D. C.

2117 Sinsheimer, J. E. & Smith, Edward. Identification of sympathomimetic amines as tetraphenylborates. *Journal of Pharmaceutical Sciences*, 52(11):1080-1083, 1963.

Tetraphenylborate (TPB) derivatives of organic bases are readily isolated in a pure form, even from low concentrations in complex mixtures. Methods are described for obtaining the melting points and spectral properties of these salts as an aid to the identification of this group of amines. Melting points of sympathomimetic amine salts are presented. The rate of formation of the TPB salts was the same as in the amperometric titration of these amines with TPB.

Food and Drug Administration
Washington, D.C.

2118 Brown, Theodore L. Spectrophotometric analysis of phenobarbital and pentobarbital in pharmaceuticals. *Journal of Pharmaceutical Sciences*, 52(3):274-275, 1963.

An analytical procedure is described for measuring the concentration of phenobarbital in mixtures of these substances (e.g., in pharmaceuticals). The method is a spectrophotometric procedure based on the shift in ultraviolet absorbance of pentobarbital following dealkylation in sulfuric acid. After either extraction, residual barbiturates are dissolved in 1.0 ml of 0.13 N sodium hydroxide and mixed with 9.0 ml of 36 N sulfuric acid. The mixture is heated for 30 minutes at 100° C, then cooled to room temperature. The sample is then placed in an ice bath and diluted to 50.0 ml with distilled water; 5 ml of this solution is mixed with 5.0 ml of 22.5% ammonium hydroxide and diluted to 100 ml with distilled water. Absorbance is measured at 240 μ and 268 μ against a reagent blank. Heating time was not critical, but the sulfuric acid concentration had to be carefully controlled. Results obtained using the analytical procedures from pure samples of the two barbiturates and from mixtures of the two are tabulated. Interfering substances were removed by filtration and solvent extraction prior to acid treatment.

Cutter Laboratories
Berkeley, California

- 2119 Marcus, Arnold D. & DeMarco, Joseph D. Method for isolation and determination of α -methyl DOPA ethyl ester in aqueous solution. *Journal of Pharmaceutical Sciences*, 52(4):402-403, 1963.

Since the ethyl ester of α -methyl-3,4-dihydroxyphenylalanine (α -methyldopa ethyl ester) in aqueous solution is subject to degradation, isolation of the totally intact ester and determination of its concentration by ultraviolet spectrophotometry seemed desirable. Separation of α -methyldopa ethyl ester from the free acid was done by column partition chromatography using 0.1 M citrate buffer (pH 4.5) adsorbed on powdered cellulose as the stationary phase and *n*-butanol as the mobile phase. The eluate was analyzed colorimetrically using a reagent specific for intact catechol nuclei in order to avoid interference by any oxidized ester. Average recovery is 98.9% of theory.

Merck Sharp and Dohme Research Laboratories
West Point, Pennsylvania

- 2120 Chin, Lincoln, Picchioni, Albert L., & Childs, Richard F. Light—an essential factor in the trihydroxyindole-spectrophotofluorometric assay of norepinephrine. *Journal of Pharmaceutical Sciences*, 52(9):907-909, 1963.

Experiments were carried out to determine the role of light in the spectrophotofluorometric assay of norepinephrine when iodine is the oxidant. Conversion of the oxidation product noradrenochrome to a highly fluorescent trihydroxyindole (THI) derivative, noradrenolutine, requires the presence of light. Light intensity of 105 foot-candles was sufficient for producing maximal fluorescence in 45 minutes of exposure; a greater intensity yielded no additional increase in fluorescence. Samples exposed to direct sunlight (8,400 foot-candles) showed a maximal fluorescence after 2 minutes of exposure. At 40 foot-candles or less, fluorescence was incomplete even though the conversion reaction was allowed 45 minutes.

University of Arizona
College of Pharmacy
Tucson, Arizona

- 2121 Petzold, John A., Camp, Walter J. R., & Kirch, Ernst R. Identification of some barbiturates in blood by use of thin-layer chromatography. *Journal of Pharmaceutical Sciences*, 52(11):1106-1107, 1963.

A simple, rapid method for identifying five barbiturates—secobarbital, amobarbital,

pentobarbital, phenobarbital, and diallylbarbituric acid—is described. The method is based on the differences in R_f values obtained after treatment of the chloroform extracts of barbiturates with 4N H_2SO_4 . The R_f values for standard stock solutions of barbiturates and for barbiturates extracted from blood are tabulated.

University of Illinois Medical Center
Chicago, Illinois

- 2122 Takeshige, Chifuyu & Volle, Robert L. Cholinceptive sites in denervated sympathetic ganglia. *Journal of Pharmacology and Experimental Therapeutics*, 141(2):206-213, 1963.

The responses to acetylcholine (ACh) of the superior cervical ganglia of cats denervated for 6 to 70 days were compared with those of a normal ganglia. The postganglionic firing evoked by ACh (2.5 μ g to 20 μ g i.a.) before and after the administration of eserine (5 μ g to 50 μ g i.a.) was the same in ganglia denervated for 6 to 13 days as that in normal ganglia. In both types of ganglia, the response consisted of a single component before eserine and of two components after eserine. The responses to ACh (1.1 μ g to 15 μ g) of untreated ganglia denervated for 14 to 28 days were characterized by two components, and eserine (up to 500 μ g i.a.) did not evoke asynchronous firing. The response to ACh (4 μ g to 20 μ g i.a.) of six out of eight ganglia denervated for 30 to 70 days consisted of a single component. Treatment with eserine (5 μ g - 50 μ g) unmasked the bimodal response to ACh. Eserine (500 μ g i.a.) produced a prolonged postganglionic discharge in ganglia denervated longer than 30 days. Just as in the normal ganglia, the eserine-induced discharge was blocked by atropine (1 μ g to 2 μ g i.a.). In all types of ganglia in which the bimodal response to ACh was demonstrated, the first component of the response was blocked by either α -tubocurarine (0.3 mg i.a.) or hexamethonium (0.3 mg i.a.), and the second component was blocked by small doses of atropine (1 μ g to 2 μ g i.a.). Repeated administrations of 1.25 mg i.a. of potassium chloride (2 or 3 at 10-minute intervals) unmasked the second component of the postganglionic response to ACh. The concept of pharmacological heterogeneity of ganglionic cholinceptive sites is supported by these findings. Some of the cholinceptive sites may be located on extrajunctional portions of the membrane of the ganglion cells.

University of Pennsylvania
Philadelphia, Pennsylvania

3 Masuoka, David T., Schott, Hermann E., & Petriello, Licia. **Formation of catecholamines by various areas of cat brain.** *Journal of Pharmacology and Experimental Therapeutics*, 139(1):73-76, 1963.

Large variations in the relative amounts of dopamine (DA) and norepinephrine (NE) have been found in sagittal slices of C^{14} -tyrosine-incubated rat brains, suggesting the possibility of variation in synthetic capacity of different areas of the brain. In order to determine to what extent variation in rates of synthesis contributes to the uneven distribution of dopamine and norepinephrine in brain tissues, slices from the hypothalamus, caudate nucleus, and the area of the visual cortex in cats were used. Histochemical identification of radioactive metabolites was made. The slices were incubated in C^{14} -tyrosine for 3 hours. Radioactive DA was found in all areas, and NE was found in the hypothalamus, visual cortex, and reticular area. The caudate nucleus formed a large quantity of DA but not NE, and the hypothalamus formed significant, but small, amounts of both NE and DA. The amount of radioactive NE and DA obtained from the hypothalamus was only 1/40 to 1/30 of that formed by the caudate nucleus. There was no obvious increase in the incorporation of radioactivity into the NE and DA fraction from the hypothalamus after pretreatment (before sacrificing) with 50 mg/kg i.p. of diazepam or with 40 mg/kg i.p. of β -nilyisopropylhydrazine. The only fraction that showed a light increase was methoxytyramine.

Neuropharmacology Research Laboratories
Veterans Administration Hospital
Fresno, California

4 Adler, Terrine K. **The comparative potencies of codeine and its demethylated metabolites after intraventricular injection in the mouse.** *Journal of Pharmacology and Experimental Therapeutics*, 139(2):155-161, 1963.

The technique of direct intraventricular injection in the conscious mouse was used to study the pharmacological effects of codeine, *O*-demethylated metabolite morphine, and *N*-demethylated metabolite norcodeine. Experiments were also performed to determine the metabolism of codeine when injected by conventional routes of administration; in this study, mice were given codeine- O - $C^{14}H_3$ or codeine-*N*- $C^{14}H_3$ s.c. By intraventricular injection, the depression of the tail-flick response to a thermal stimulus required doses of codeine more than 100 times

larger than for morphine. The effects of morphine were antagonized by pretreatment with nalorphine, but the effects of codeine were not. Norcodeine resembled codeine in its effect on the tail-flick response with respect to both the size of the dose required and the pharmacologic indifference to nalorphine. Norcodeine, however, was about six times more toxic than codeine and about twice as toxic as morphine similarly injected. In no case was toxicity reduced by pretreatment of the mice with nalorphine, and no antagonism between codeine and morphine was seen in any of the effects studied. When codeine was given s.c. in mice, the major pharmacologic effects were achieved only after the release and distribution of its demethylated metabolites.

University of California Medical Center
San Francisco, California

2125 Douglas, J. F., Ludwig, B. J., & Smith, Nancy. **Studies on the metabolism of meprobamate.** *Proceedings of the Society for Experimental Biology and Medicine*, 112(2):436-438, 1963.

Urinary excretion ratios of meprobamate and hydroxymeprobamate in the rat, dog, mouse, rabbit, guinea pig, and human beings are summarized. Animals were administered meprobamate by several routes, the dosage varying from 40 mg/kg to 200 mg/kg. The urine was collected under toluene for 24 hours, and aliquots were chromatographed directly. The relative concentration ratios of hydroxymeprobamate to meprobamate excreted at 6 and 24 hours after drug administration were in excess of 2:1, and in some cases, 7:1. Different routes of administration did not affect the ratio. Human subjects received either 1,200 or 1,600 mg of meprobamate over a single 18-hour period or received the same daily dose for periods in excess of a month. Aliquots of urine collected were again chromatographed directly. The single-day human subjects had a ratio of about unity (0.9:1), whereas the other group exhibited a corresponding ratio of 1.8:1. These values were substantially lower than those found in the animals. Chronic administration of meprobamate to human beings thus appears to stimulate its metabolism.

Wallace Laboratories
Division of Carter Products, Inc.
Cranbury, New Jersey

- 2126 Woohsmann, H. Ein Beitrag zur monoaminoxidase des zentralnervensystems. (A study of monoaminoxidase in the central nervous system.) Acta Biologica et Medica Germanica, 11(2):164-168, 1963.

Adult white rats were decapitated, and the brain and liver sections were prepared with nitro-BT following the method of Burner and Brown. Noradrenaline, adrenaline, tryptamine, and serotonin substrates were tested with incubation media for oxidation in the creatinin sulfa compounds. Tyramine, dopamine, mescaline, putreszine, histamine, benzylamine, butylamine, isobutylamine, and β -naphthylamine were also tested. Bitartrate of noradrenaline and adrenaline were demonstrated to be of substantially stable bases. Dopamine oxidized very slightly. Serotonin in the 5-hydroxy group did not oxidize easily. The 3-hydroxy compounds with tyramine demonstrated the longest incubation period before breakdown. The substrates demonstrated little chemical difference. By the light oxidation of the substrates of serotonin and dopamine, the author demonstrates the supposition that MAO occurs in the CNS in the two types—serotonin oxydase and dopamine oxydase. The metabolism of adrenaline and noradrenaline by the MAO in the CNS could not be proved by tetrazolium salts.

Germany Academy of Science
Berlin, Germany

- 2127 Gupta, R. C. & Kofoed, J. Separation, purification and identification of some common barbiturates in toxicological analyses. Nature, 198(4878):384, 1963.

Since barbiturates isolated from biological fluids and tissues are not sufficiently pure for characterization by crystal tests, a combination of paper chromatography and sublimation was used successfully. A description is given of this method, which was used in isolating microquantities of barbiturates from blood and from other biological specimens.

Attorney-General's Laboratory
Toxicology Section
Toronto, Canada

- 2128 Seeman, Philip M. Sodium - potassium-activated adenosine triphosphatase in schizophrenic erythrocytes. Nature, 200(4903):263-264, 1963.

On the assumption that schizophrenia may be

a disease of cell excitability, sodium—potassium—adenosine triphosphatase (Na-K-ATPase), a membranal enzyme intimately associated with cell excitability, was investigated in the erythrocyte membranes of four normal volunteers and six subacute paranoid schizophrenics. Enzyme assay was performed by the method of Bonting et al. (1961). The mean Na-K-ATPase for normals was 35.2 ± 11.6 μ moles ATP split/hour/mg dry weight; the value for the schizophrenics was 79.1 ± 14 . Residual ATPase was 180 ± 10 for normals and 246 ± 90 for schizophrenics. Two of the patients had received tranquilizers the week preceding the test. It is suggested that Na-K-ATPase measurements be made on more subjects before conclusions are drawn.

The Rockefeller Institute
New York, New York

- 2129 Inouye, Akira, Kataoka, Kiyoshi, & Shinagawa, Junko. Uptake of 5-hydroxytryptamine by sub-cellular particles of rabbit brain. Nature, 198(4877):291-293, 1963.

The effects of incubation temperature, pH, concentration of 5HT, and the addition of various compounds to the incubation media on the 5HT uptake in rabbit brain were investigated. In some experiments, the 5HT uptake of nuclear, mitochondrial, microvesicular, and microsomal fractions was compared; in other experiments, the combined particulate fraction, excluding nuclei and the cytoplasmic supernatant, was used. The 5HT content of all four fractions increased at 4° C if the 5HT concentration of the suspending medium was sufficiently high, but at 45° C, the 5HT content decreased, even when large amounts of 5HT were present in the medium. Optimum pH at 4° C and 37° C was 7.0 to 7.5. Addition of dinitrophenol, cyanide, *p*-chloromercuribenzoate, and adenosine triphosphate (all at 1 mM) and cysteine had no effect on 5HT uptake in the combined fraction. Oxidized glutathione, insulin, or vasopressin (1.25 to 1.67 mM) caused a slight increase. Potassium ion (100 to 200 mM) depressed 5HT uptake, but calcium and magnesium ions (10 to 200 mM) and reserpine (500 μ g/ml) had no effect. Experiments on the mechanism of 5HT uptake are also discussed, but no conclusions are drawn.

Kyoto University
Kyoto, Japan

130 Gal, Emery M. **Psychiatry. Cholinesterase activity of whole blood from healthy and schizophrenic individuals.** *Nature*, 198(4885):1118-1119, 1963.

This communication reports information concerning cholinesterase activity of whole blood in schizophrenics as compared to that of healthy individuals. The population analyzed consisted of 169 "healthy" individuals (nurses, clerks, and laborers), of which 50% were males, and 76 schizophrenics, of which 89% were males. None of the subjects had previous medication. The cholinesterase activity was analyzed spectrophotometrically. Increased blood cholinesterase activity was observed in schizophrenics, and female schizophrenics showed higher values of cholinesterase activity than males. In the "healthy" sample, males showed higher cholinesterase activity. Age and race did not show correlation to differences in cholinesterase activity in the whole blood. Increased blood cholinesterase activity in schizophrenics should not be construed as proof in signing a direct responsibility to cholinesterase as a causative factor for the behavioral characteristics of schizophrenics.

Veterans Administration Hospital
Pulveda, California

31 Friedhoff, Arnold J. & Van Winkle, Elnora. **Conversion of dopamine to 4-dimethoxyphenylacetic acid in schizophrenic patients.** *Nature*, 199(4900):1271-1272, 1963.

Experiments were performed to determine whether 3,4-O-methylation of dopamine occurs in schizophrenic patients. Five hospitalized schizophrenics were given 200 μ c of dopamine-7H³ hydrochloride, and their urines were then collected for 3 hours. Urines from three patients were analyzed separately, and urines from two patients were pooled. Chromatograms of the aqueous phase of a chloroform extract revealed peaks corresponding to 4-hydroxy-3-methoxyphenylethylamine and 3,4-dimethoxyphenylethylamine. The organic phase showed peaks corresponding to 4-hydroxy-3-methoxyphenylacetic acid and 4-dimethoxyphenylacetic acid. Homogenized liver tissue from one of the patients was incubated with 0.60 μ M of dopamine-7H³ hydrochloride. Chromatograms of chloroform extracts revealed peaks corresponding to 4-hydroxy-3-methoxyphenylacetic acid and 4-dimethoxyphenylacetic acid.

New York University School of Medicine
New York, New York

2132 Horovitz, Zola P., Furgiuele, Angelo R., Brannick, Leo J., Burke, John C., & Craver, Bradford N. **A new chemical structure with specific depressant effects on the amygdala and on the hyperirritability of the 'septal rat'.** *Nature*, 200(4904):369-370, 1963.

The compound 5-(2-dimethylaminoethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one HCl (SQ 10,496) was investigated for its effects on the electrical afterdischarge produced by stimulation of various areas in the limbic system of the cat. Stimulation (50 cps for 2.0 milliseconds) of each of the three limbic areas of the freely moving, unanesthetized cat produced an electrical afterdischarge recorded in other limbic areas and in parts of the cortex. At doses of 5.0 to 12.0 mg/kg, SQ 10,496 depressed amygdaloid output but had no effect on the arousal threshold of the reticular formation or on the spontaneous electrical activity of the cortex and hypothalamus. SQ 10,496 was found to antagonize the hyperirritability exhibited by rats with bilateral lesions of the septal area, but had no effects on normal rats. The effects of SQ 10,496, chlorpromazine, chlordiazepoxide, and pentobarbital on rat rotarod performance and on the rage response in rats with bilateral lesions of the septal area are tabulated.

Squibb Institute for Medical Research
New Brunswick, New Jersey

2133 Oyvin, I. A., Shegel, S. M., & Yagodka, E. G. **Influence on capillary permeability of lymph discharged from a scald.** *Nature*, 200(4903):270-271, 1963.

The pressor effects of hordenine, hordenine methiodide, the trimethylammonium derivatives of dopamine and of noradrenaline, ethyltrimethylammonium bromide, and choline chloride were studied in spinal-catheter preparations. Nicotine-like action was greatly reduced in those compounds with an -OH group attached to the β -carbon atom.

May and Baker Ltd.
Dagenham, Essex, England

2134 Diamond, J. **Variation in the sensitivity to gamma-aminobutyric acid of different regions of the Mauthner neurone.** *Nature*, 199(4895):773-775, 1963.

In this article, regional differences in the chemical sensitivity of the Mauthner neurone are described and tentatively correlated

with known morphological and functional features. The substances tested, GABA and L-glutamic acid, were applied to the cell membrane of goldfish ionotophoretically from micropipettes. Antidromic excitation and orthodromic activation of the Mauthner cells were produced by wire electrodes. *d*-Tubocurarine (i.m. injection) prevented movement caused by the Mauthner cell excitation. The recording electrode was usually inserted in the cell body, while the drug-electrode position varied. During the effects of GABA, there was no change in membrane resting potential when a potassium sulfate electrode was used, but, with a potassium chloride electrode, GABA caused a depolarization. Records made with the drug pipettes in the lateral dendrite (distal part) showed a difference from those in the cell body in sensitivity to GABA, but not to glutamate. An internal electrode within 75 μ of the distally located drug pipette failed to detect a response to GABA, the response to glutamate being normal. The threshold charge for glutamate was usually constant from region to region and cell to cell. The variation in sensitivity to GABA of the Mauthner cell membrane may be correlated with other known features. The GABA-insensitive region corresponds with that which receives the large-club endings of the ipsilateral VIII nerve. The axon-hillock, cell body, and proximal part of the lateral dendrite are all inhibited by GABA and receive fibers from the contralateral VIII nerve.

Harvard Medical School
Boston, Massachusetts

the ethylacetate fraction to dryness, and determining the UV spectrum by redissolving the residue in methanol. Phenobarbital (15 mg q.i.d.) is detected by extraction of acid urine with chloroform, washing with phosphate buffer, extraction with sodium hydroxide, and then determination of the UV spectrum. By a rapid color test in which 1 ml of test solution (5 parts 5% ferric chloride, 45 parts 20% perchloric acid, and 50 parts 50% nitric acid) is added to 1 ml of urine, the phenothiazines (20 mg) can be detected by the color change that occurs within 30 seconds. Chlorpromazine may be detected on the basis of the UV absorption spectrum of its metabolite, chlorpromazine sulfoxide.

USAF School of Aerospace Medicine
Brooks Air Force Base, Texas

See also: 2042, 2049, 2050, 2088

2135 Foft, John W. & Williams, Robert J.
Clinical problems in aviation
medicine: Laboratory methods for the
detection of antihypertensive drugs in
flying personnel. Aerospace Medicine, 34:
948-950, 1963.

A method for detecting antihypertensive drugs in the urine of persons who have received known therapeutic doses of some of the antihypertensive agents is described. Chlorothiazide may be detected in the urine 24 hours after administration of 500 mg by extracting 10 ml of acid urine (pH 4 or below) with 50 ml of ethylacetate, washing the acetate layer with phosphate buffer, extracting with sodium hydroxide, and determining the ultraviolet (UV) spectrum. Hydrochlorothiazide may be detected in the urine 8 hours after an oral dose of 50 mg by extraction with ethylacetate, evaporating

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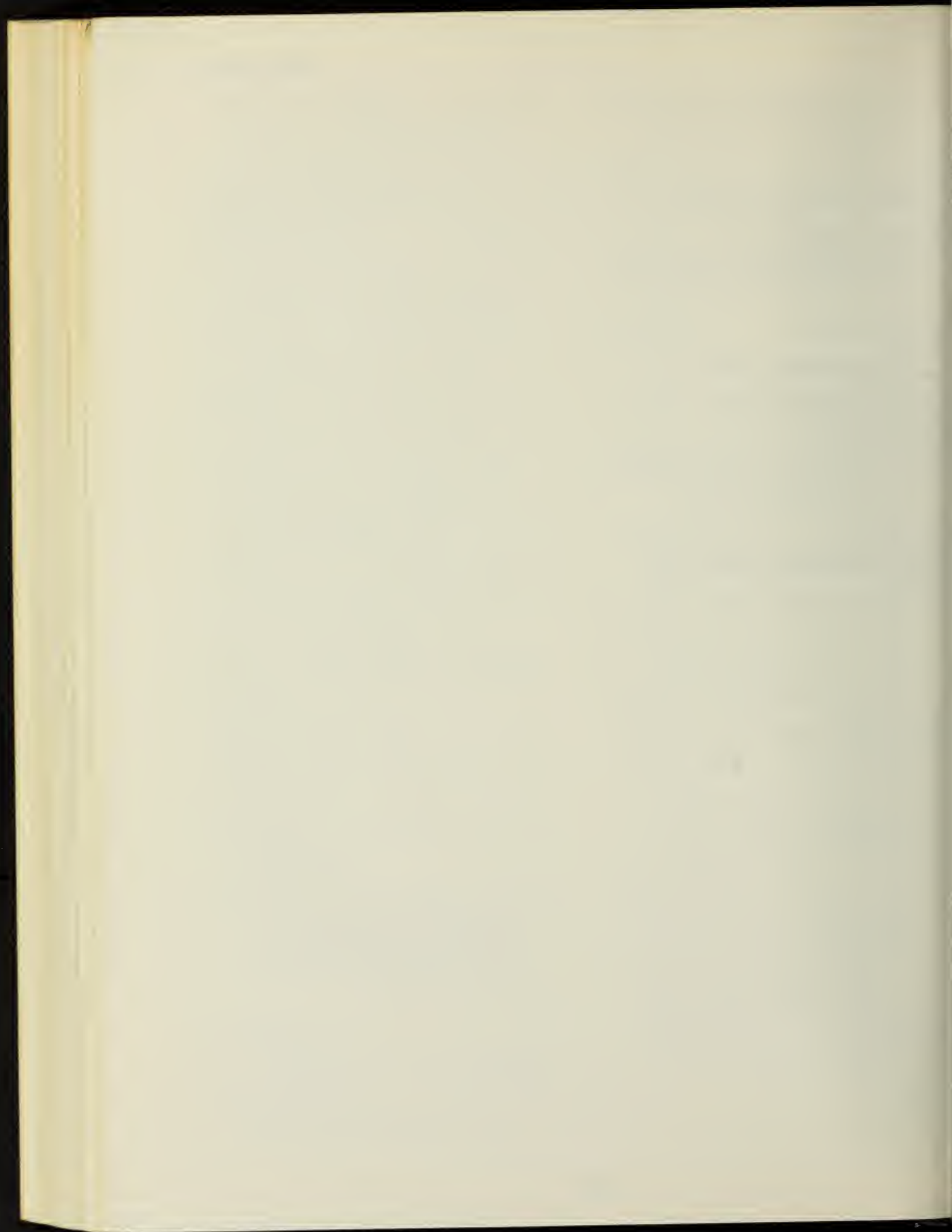
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PSYCHOPHARMACOLOGY ABSTRACTS

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PSYCHOPHARMACOLOGY ABSTRACTS

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REVIEWS, SUMMARIES, BIBLIOGRAPHIES, GENERAL ARTICLES AND BOOKS

- 2136 Central Neuropsychiatric Research Laboratory. **Cooperative studies in psychiatry.** Report on the right drug for the right patient. Klett, C. James & Moseley, Edward C. Perry Point, Maryland, November 1963, 13 p.

In selecting the right drug for the right patient, evaluation of the drug is based on the specific and selective action of the drug. Multiple regression equations were developed for schizophrenic patients who had received chlorpromazine, fluphenazine, and thioridazine, using 10 pretreatment syndrome scores to predict drug response and 3 posttreatment morbidity scores as the criteria of drug effectiveness. The drug associated with the equation that gave the most favorable prediction could be considered the "drug of choice." Patients receiving their "drug of choice" showed superior response to treatment. Random assignment of patients to the different drugs would have led to an acceptance of the null hypothesis.

Central Neuropsychiatric Research
Laboratory
Veterans Administration Hospital
Perry Point, Maryland

- 2137 McLaughlin, B. E. **Recognition and treatment of nonpsychotic depression in office practice.** Journal of the American Medical Women's Association, 18(10):802-807, 1963.

Nonpsychotic depression is discussed from the standpoint of early recognition and treatment. The key to the earliest possible recognition of depression by the clinician is based on the transference concept. Three examples are given showing a disturbance of the established transference between patient and physician. The antianxiety compounds are being used more and more to create and maintain successful transference. The family and community are also resources of support in treating the depressed nonpsychotic patient. When the mechanisms that are practically possible within office treatment fail, such as the administration of tranlycypromine

10 mg b.i.d. or t.i.d. and trifluoperazine 2 mg b.i.d. or t.i.d., depressed patients should be referred to a psychiatrist.

Women's Medical College of Pennsylvania
Philadelphia, Pennsylvania

- 2138 Esplin, Don W. **Criteria for assessing effects of depressant drugs on spinal cord synaptic transmission, with examples of drug selectivity.** Archives Internationales de Pharmacodynamie et de Therapie, 143(3-4): 479-497, 1963.

This report is concerned with the use of spinal synaptic systems as material models for assessing the effects of depressant drugs because of their great diversity of function and because of the vast amount of physiological information concerning spinal cord function. A new experimental design is described in which a specific aspect of transmission is studied at various levels of excitability as influenced by a change in spinal cord temperature. The effect of a drug on this aspect of synaptic transmission is examined over the same range of excitabilities during drug depression. The differential effects of depressant drugs on synaptic recovery, posttetanic potentiation (PTP), and response during repetitive stimulation were discussed. Analysis of the effects of a number of depressant drugs indicates that excitation, synaptic recovery, and PTP are capable of discrete pharmacological manipulation, thus revealing at least three distinct facets of depressant action, one or more of which may be possessed by a given drug.

University of Utah College of Medicine
Salt Lake City, Utah

- 2139 Shapiro, Shepard. **Angina pectoris—An effective therapeutic approach.** Clinical Medicine, 70:1627-1636, 1963.

The etiology and management of patients with angina pectoris are discussed. Emotional problems are important contributing and

precipitating factors of the disease. Emotional stress of the angina patient may result from personal problems independent of the disease or anxiety as a result of the patient's awareness of the threat to his life presented by his coronary condition. Physiological and psychological therapy is used in treating angina patients. A long-acting nitrite, pentaerythritol tetranitrate (PETN), is most effective in prophylactic treatment. The use of a meprobamate with this drug is advisable to cushion the impact of emotional tensions. Diet management and limited physical activity should also be employed. One hundred patients were treated with meprobamate, PETN, and psychotherapy or supportive measures and, of these, 51 patients returned to near normal productivity and 45 to limited activity.

New York, New York

- 2140 Kandrac, M. S. *Metabolismus a biochemie adrenalinu a noradrenalinu. (Metabolism and biochemistry of adrenaline and noradrenaline.)* Časopis Lékařů Ceškých, 101(50):1468-1478, 1963.

Recent data published in the literature on the metabolism of adrenaline and noradrenaline in man and animals are summarized. The mechanism of *O*-methylation, oxidative deamination, conjugation, and the interaction of the catecholamines with certain nucleotides are described. Some general problems in studying the metabolism of the β -phenylethylamine-type biogenic amines and projected research are discussed. (60 references)

Comenius University
Prague, Czechoslovakia

- 2141 Robie, Theodore R. *Anti-depressant drug combinations.* Journal of the Medical Society of New Jersey, 58:1-8, 1962.

Combinations of drugs were discussed as useful measures in the treatment of depressed patients. Special attention was given to depression associated with malnutrition. Some of the drug combinations discussed are as follows: methylphenidate—iproniazid, chlordiazepoxide—MAO inhibitors, and pyridoxine—iproniazid.

East Orange, New Jersey

- 2142 Poser, Charles M. *International dictionary of drugs.* Springfield, Charles C. Thomas, 1962. 157 p.

In the hope that standard drug names will be adopted universally, this dictionary supplies for many pharmacological agents the generic names, trade names, common names, trivial names, and alternate chemical designations, as well as the countries using these terms. No drug mixtures or combinations are included; only those drugs with a single active ingredient are given. Anesthetic agents, antihistamines, and analgesic drugs are also included.

University of Kansas School of Medicine
Kansas City, Kansas

- 2143 Frommel, Ed., v. Ledebur, I., & Beguin, M. *The psychopharmacological properties of acetylsalicylic acid and cortisone.* Arzneimittel-Forschung, 13(11):945-949, 1963.

The psychopharmacological aspects of acetylsalicylic acid and cortisone were found to be expressed sometimes by a depressive action and sometimes by an excitatory amphetamine-like effect. It was not possible to determine the respective places occupied by these two substances in the classification of the psychopharmacological drugs since they have not been differentiated and characterized.

Institute of Experimental Therapeutics
of the Geneva University School of
Medicine
Geneva, Switzerland

- 2144 Hasting, Glen E. *Monoamine oxidase inhibitors: A review.* Journal of the Kansas Medical Society, 64:409-418, 1963.

A discussion is given of MAO inhibitors in terms of their clinical efficacy, their commercial availability, their side effects, and their pharmacological actions with correlation between experimental and clinically observed phenomena.

University of Kansas Medical Center
Kansas City, Kansas

- 2145 Vencovský, E. *Kritické poznámky k farmakoterapii deprese.* (Critical notes on the pharmacotherapy of depression.) *Ceskoslovenska Psychiatrie*, 59:151-158, 1963.

Drug treatment of depressive states is discussed. Antidepressant drugs are divided into the following three groups, based partly on chemical composition and partly on mode of action: (1) neuroleptics—thioridazine, levomepromazine, and chlorprothixene; (2) thymoleptics—imipramine, amitriptyline, and trimipramine; and (3) MAO inhibitors—nialamide, iproniazid, and phenelzine. Drugs of groups 1 and 3 may be combined safely, but combining drugs of groups 2 and 3 is contraindicated. The use of drugs alone in the treatment of all other forms of psychosis is substantially more effective than the use of drugs alone in the treatment of depression. The ECT cannot be discarded as yet as a therapy for depression. Most effective results are achieved with a combination of ECT and drug therapy.

Comenius University
Plzen, Czechoslovakia

- 2146 Piette, Y. *Mécanismes d'action des drogues psychotropes.* (Mechanism of action of psychotropic drugs.) *Bruxelles-Médical*, 43(4):93-108, 1963.

Various systems for classifying the psychotropic drugs are discussed. The system proposed by Delay and Deniker (1961), based on the pharmacological properties of the drugs rather than on their chemical structure, is presented as the most logical and practical one for the physician. The system consists of the following: (1) psycholeptics, or psychic sedatives—hypnotics, neuroleptics or thymoleptics, and tranquilizers; (2) psychoanaleptics, or psychic stimulants—psychotonic amines, thymoanaleptics, and miscellaneous stimulants, such as vitamin C; and (3) psychodysleptics—hallucinogenic agents and drugs inducing depersonalization. Another concept of classification developed by Hess and by Brody is based on two subcortical systems, the ergotropic and trophotropic systems, which are mutually antagonistic. The ergotropic system stimulates the sympathetic system and increases motor activity and muscle tonus. Drugs can be classified according to their actions on these systems. The action of various drugs on these systems is described.

Ostende, Belgium

- 2147 Society for the Study of Higher Nervous Activity. *Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity*, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963. 359 p. (Psychopharmacological methods.)

Proceedings of a symposium on the effects of psychotropic drugs on higher nervous activity have been outlined in the form of a table of contents.

Charles' University
Medical Faculty of Hygiene
Prague, Czechoslovakia

- 2148 Sidman, Murray. *Some technical problems in evaluating the behavioral effects of drugs.* In: Society for the Study of Higher Nervous Activity. *Proceedings of a symposium on the effects of psychotropic drugs on higher nervous activity*, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 162-169. (Psychopharmacological methods.)

Several large areas of research are involved in the study of the influence of psychotropic drugs on higher nervous activity. Investigators in any one of these areas (pharmacology, physiology, biochemistry, or psychology) may encounter problems when they attempt to use behavioral phenomena as one dimension of their research. The approaches to and problems in classifying behavioral phenomena are discussed.

Massachusetts General Hospital
Boston, Massachusetts

- 2149 Ferster, C. B. & Appel, J. B. *Interpreting drug-behavior effects with a functional analysis of behavior.* In: Society for the Study of Higher Nervous Activity. *Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity*, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 170-181. (Psychopharmacological methods.)

The results of experiments that measured the effects of drugs on operant behavior are discussed. Pigeons were used in experiments with amobarbital, pentobarbital, and chlorpromazine. It was concluded that the effect of a drug should

be viewed as due to its effect on some functional relation between the behavior of the individual and the controlling variable in the environment or environmental history.

Indiana University Medical Center
Bloomington, Indiana

- 2150 Lehman, H. E. **Problems of evaluation and classification in psychopharmacology.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 276-280. (Psychopharmacological methods.)

A method of evaluating and classifying drugs, which attempts to retain the advantages of the clinical approach, has been proposed. The shortcomings of the descriptive and empirical target-symptom approach have been avoided by orientation of the method on three functional parameters (arousal, affect, and integration) with established neurophysiological representation.

Verdun Protestant Hospital
Verdun, Quebec, Canada

- 2151 Kuhn, E., Rysánek, K., Vitek, V., Vojtěchovský, M., & Grof, S. **Multidimensional approach to the psychopharmacological experiment.** Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 281-301. (Psychopharmacological methods.)

This paper surveys the methodical gains of a group of authors who work in various fields, and aims at determining the clinical, physiological, and metabolical criteria that would give the most complete and complex information to be gained from the research data on the results of applying psychotropic drugs. The determination of the inhibitive influence on MAO by drugs was done in vivo and in vitro. The reliability of the respective procedures is discussed, as well as their limitations and imperfections.

Research Institute for Human Nutrition
Praha-Krc, Czechoslovakia

- 2152 Vondráček, V. **Contribution of a clinician.** Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 357-358. (Psychopharmacological methods.)

The evaluation of psychotropic drugs in "major" and in "minor" psychiatry is discussed. Evaluation was found to be much easier and more accurate in "major" psychiatry because of the larger number of factors involved in "minor" psychiatry.

Charles University
Prague, Czechoslovakia

- 2153 Haškovec, V. **Contribution of microscopical anatomy.** Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 359-360. (Psychopharmacological methods.)

The study of the effect of drugs is discussed from the point of view of experimental morphology. It is concluded that the therapeutic effect of psychotropic drugs may be determined by morphology, together with electron microscopy and other qualitative and quantitative histological methods.

Psychiatric Research Institute
Prague, Czechoslovakia

- 2154 Leigh, Denis. **Advances in psychiatry.** Practitioner, 191:431-442, 1963.

A review is presented of advances in psychiatry, with emphasis on work in the clinical field. Psychosurgery, leucotomy, drug therapy, behavior therapy, psychosomatic medicine, and forensic psychiatry are discussed in terms of their advantages and disadvantages.

Bethlem Royal and Mandsley Hospitals
London, England

- 2155 Robson, J. M. **The problem of teratogenicity.** Practitioner, 191:136-142, 1963.

The problem of teratogenicity is discussed in terms of those teratogenic effects that arise independently of the action of drugs

and of those effects that are specifically produced by drugs. Experimental effects with thalidomide and with other drugs in common use that probably are not teratogenic in man are reported. Evidence is also presented that 5HT may be a factor in the production of abnormalities that arise independently of the administration of drugs.

Guy's Hospital Medical School
London, England

- 2156 Simpson, John A. **The drug treatment of parkinsonism.** Practitioner, 191:360-365, 1963.

The nature of parkinsonism, as well as drug therapy, surgical treatment, and general management is discussed. Some current synthetic spasolytics used in the treatment of parkinsonism, their dosages, and side effects are listed.

University of Edinburgh
Edinburgh, Scotland

- 2157 Beavers, W. R. **Evaluating drugs used in emotional illness.** Texas State Journal of Medicine, 59:844-847, 1963.

The problems encountered in studies of the relative effectiveness of drugs for the treatment of emotional illnesses are discussed. Antidepressants and tranquilizers (phenothiazines) were compared, and conclusions were reached on the basis of the best evidence available.

University of Texas Southwestern Medical School
Dallas, Texas

- 2158 Charalampous, K. D. & Kinross-Wright, John. **Hallucinogens. Tools for research or therapeutic agents.** Texas State Journal of Medicine, 59:848-852, 1963.

The drugs LSD, mescaline, and psilocybin (hallucinogens) have similar properties, which are discussed. They belong to one family and are characterized by similarities in chemical structure and sympathomimetic effects. The superficial similarity of the effects of these drugs in the schizophrenic has stimulated research into the etiology of schizophrenia. Undesirable side effects that may follow their use or application are included.

Baylor University
College of Medicine
Houston, Texas

- 2159 Parr, Denis. **Problems in the appraisal and use of tranquilizers, analgesics and hypnotics.** In: Williams, Denis, ed. *Modern trends in neurology.* Washington, Butterworths, 1962, p. 336-352.

The progress that has been made toward identifying personality factors relevant to drug action and rendering them more accessible to statistical control in clinical experiments is discussed. Brief reference was made to two points of interest of recent work in this field (placebo reactors and sedation threshold), after which particular consideration was given to tranquilizers, analgesics, and hypnotics.

St. George's Hospital
London, England

- 2160 Smythies, J. R. **Hallucinogenic drugs.** In: Williams, Denis, ed. *Modern trends in neurology.* Washington, Butterworths, 1962, p. 353-366.

The mode of action of several hallucinogenic drugs is discussed. Particular consideration is given to LSD, its effects on animal behavior, on electrical activity of the brain, and on cholinesterases. Brief reviews of experiments conducted with mescaline, hallucinogenic derivatives of tryptamine, and amphetamine are also included.

St. George's Hospital
London, England

- 2161 Mautner, H. **Drug treatment and brain physiology.** In: Stur, Otto, ed. *Part II. Psychological and sociological problems in imbecility drug treatment. Proceedings of the Second International Congress on Mental Retardation.* August 14-19, 1961. Basel, Switzerland, Karger, 1963, p. 119-127.

Drug treatment and brain physiology, one of the papers presented at the Second International Congress on Mental Retardation, is discussed. A survey of the literature concerning brain function was followed by a general discussion of drugs (glutamic acid, ephedrine, and MAO inhibitors) that have been used for improvement of mental development.

Pownal, Maine

2162 Diesing, U. *Padiatrische Erfahrungen mit Librium. (Experiences with Librium in pediatrics.)* In: Stur, Otto, ed. Part II. Psychological and sociological problems in imbecility drug treatment. Proceedings of the Second International Congress on Mental Retardation. August 14-19, 1961. Basel, Switzerland, Karger, 1963, p. 128-130.

Chlordiazepoxide was given to 144 children undergoing treatment for nocturnal enuresis, scholastic difficulties, or brain damage. The group of enuretics, consisting of 58 selected refractory cases, was given placebo for 1 to 6 weeks under double-blind conditions. The patients that did not improve under placebo were given 10 to 25 mg/day chlordiazepoxide in the evening. The study covered a total of 4,656 patient-nights, averaging 80 nights/child. Bedwetting occurred on 87% of the nights before treatment; this percentage dropped to 43% under placebo, and 18% under chlordiazepoxide. In a matched control group of 67 patients given psychotherapy, drug or physical therapy, bedwetting dropped from 88% to 24%. In another control group of 42 patients given no treatment, the frequency of bedwetting dropped from 76% to 24% over a 1-year period. In the chlordiazepoxide group 76% of the patients improved. The drug was successful in 43% of the patients under 6 years of age, in 78% of those 6 to 9 years of age, in 91% of those 10 to 14 years of age, and in 100% of the adolescent group. Twenty-nine children with scholastic difficulty were given 10 to 20 mg/day chlordiazepoxide, and improvement was obtained in eight cases. In the 27 children with brain damage, a dose of 20 to 30 mg/day resulted in improvement in motor unrest in 15 of 20 children and improvement in the lability of mood in 9 out of 13 cases; no change in intellectual capacity was observed. Side effects consisted of a drop in muscle tonus in one case, and excessive increase in appetite and weight gain in five cases.

Hamburg, Germany

CLINICAL STUDIES

- 2163 Schmiede, Gustav R., Jr. **LSD as a therapeutic tool.** Journal of the Medical Society of New Jersey, 60(5):203-207, 1963.

The following two therapeutic uses of LSD are described: (1) It may be used, in small multiple doses, as a psychoadjuvant to facilitate psychotherapy. (2) The drug may be used to elicit psychedelic experience when one large dose is given. The LSD has been successful in the treatment of personality disorders, alcoholics, and obsessive compulsives. Rates of effectiveness of LSD would be higher if the subjects treated were not very ill. The drug is often used in patients who have not responded to other therapies. A discussion of several studies on the use of LSD is presented. Many therapists have found that LSD speeds psychotherapy in neurotics, but has been disappointing in schizophrenics. If given under proper supervision, LSD appears to be safe.

Carrier Clinic
Belle Meade, New Jersey

- 2164 Benham, William H. **A clinicopathological conference.** Ohio State Medical Journal, 59:822-826, 1963.

The case of a 66-year-old white woman, a known alcoholic for 8 to 10 years before hospitalization, is presented. The patient was comatose at the time of admission, and died 2 days later. Alcoholism is discussed in terms of the production of multiple toxins and multiple deficiencies.

Ohio State University Hospital
Columbus, Ohio

- 2165 Krakowski, A. J. **Chlordiazepoxide in treatment of children with emotional disturbances.** New York State Journal of Medicine, 63(23):3388-3392, 1963.

The preliminary study of the evaluation of the effects of chlordiazepoxide on various states of emotional disturbance in children is reported. The subjects, 51 children and

adolescents (40 boys and 11 girls, mean age 10 years), were given chlordiazepoxide at an initial dose of 15 mg p.o., after which, doses were adjusted on an empirical basis. The largest daily dose was 60 mg, and the maintenance dosage ranged from 5 to 40 mg, with the mean dose being 26 mg. Marked or good remission of symptoms was observed in 66.6% of the total sample. The improvement was greatest in the patients with neurotic reactions (6 cases), followed by those patients who displayed adjustment reactions of childhood with neurotic habits and conduct disorders (22 cases), and finally by mental retardees with behavior reactions (12 cases). It was observed that concurrent psychotherapy and cooperation of the parents increased the beneficial effects of the drug. Side effects were present in a small number of patients, and only one patient had to discontinue the drug because of severe sleepiness. It was concluded that chlordiazepoxide was quite useful in the treatment of emotionally disturbed children, and that when the disorganizing symptom was controlled, the child adjusted better to his environment.

Plattsburgh Child Guidance Center
Plattsburgh, New York

- 2166 Litkewitsch, Helene. **Antidepressant-tranquilizer regimen in menopausal patients, drug report.** Journal of the American Medical Women's Association, 18(10): 819, 1963.

The results of a clinical trial are reported in which 32 menopausal patients (42 to 59 years of age) were given tablets containing tranlylcypromine (10 mg b.i.d.) and trifluoperazine (1 mg b.i.d.). At the end of 2 weeks, 27 (84%) were much improved. It appeared that tranlylcypromine was effective in managing the elements of depression in menopausal patients. A combination of the two drugs was well tolerated.

St. Paul, Minnesota

2167 Crownsville State Hospital.

Research report on the effects of procaine on a group of geriatric patients. Johnson, Archer, C., Jones, Roy J., Riddick, Walter E., & Deshields, Jafes I. Crownsville, Maryland, February 1963, 35 p. Typed.

The effects of i.m. injections of procaine HCl were determined on a selected group of 48 male Negro and 48 female Negro patients with a diagnosis of chronic brain syndrome, associated with cerebral arteriosclerosis or with senile brain disease. All patients were 60 years of age or over, showed no sensitivity to an intradermal injection of 0.2 cc of a 2% solution of procaine HCl, and were not blind, deaf, or nonambulatory. Forty-eight of the patients (24 males and 24 females) were given 5 cc of a 2% solution of procaine HCl 3 times a week and the remaining 48 were given 5 cc of normal saline solution i.m. 3 times a week. Nine courses of medication were given over a 342-day period, followed by a postmedication period of 76 days. Procaine patients and placebo patients were compared by physical, neuropsychiatric, and ward adjustment measures before, during, and after the medication period. No significant differences were found between the groups in the graded physical characteristics, in the neurological data, or in ward behavior. There were four deaths in the drug group and six deaths in the control group. It was concluded that procaine is not an effective eutropic or rejuvenating agent.

Crownsville State Hospital
Crownsville, Maryland

2168 Levine, Jerome, Ludwig, Arnold M., & Lyle, William H. **The controlled psychedelic state.** American Journal of Clinical Hypnosis, 6(2):163-164, 1963.

In order to channel many of the unstructured aspects of the psychedelic state in a more therapeutic direction, hypnosis was used in conjunction with LSD-25. Patients who were narcotic addicts, but who had been completely withdrawn from any drugs for a considerable time were used. During the first session, an interview was conducted, and the patients were trained in hypnosis. In the second session, the patient was given LSD-25 100 to 150 mg p.o. in distilled water. Within the 30- to 60-minute period before the drug began to take effect, the patients were hypnotized and then encouraged to examine and understand their current difficulties in context with past experiences and relationships. The patients were

brought out of the hypnotic state in about 3 hours and given posthypnotic suggestions as an aid to help them remember what occurred during the session and to continue working on their problems.

U.S.P.H.S. Hospital
Lexington, Kentucky

2169 Pavoni, M. & Pavoni-Montanari, L. **Possibilita' terapeutiche di un nuovo farmaco ad azione anti-depressiva.** (Therapeutic possibilities of a new drug with antidepressive action.) Rassengna di Studi Psichiatrici, 51:601-610, 1962.

The antidepressant Ganassini Adepressina was tested for its therapeutic effect in 42 depressives, 15 males and 27 females, 16 to 67 years of age. Diagnoses included 27 psychoneurotic depressives, 12 reactive depressives, 2 involutional depressives, and 1 endogenous depressive. The drug was given in liquid or tablet form in doses of 4 to 8 tablets daily or 30 drops t.i.d. or q.i.d. for 10 to 20 days. Clinical results were assessed with the Pfister color pyramid test. Results were excellent in 11 subjects, good in 11, moderate in 5, and slight in 8, and 7 patients showed no change in condition. Changes in response to the various colors in the Pfister test are listed for each patient.

University of Ferrara
Ferrara, Italy

2170 Levin, J., Trafford, J. A. P., Newland, P. M., & Bishop, P. M. F. **Chlorphentermine in the management of obesity.** Practitioner, 191:65-69, 1963.

The effect of chlorphentermine on weight loss was investigated in a double-blind trial, using 25 obese patients selected from an endocrine clinic. There were 19 females and 6 males, with an average age of 24.4 years. The dosage varied from 75 mg/day to 50 mg/day in 13- and 14-year-old patients. An evaluation was made at the end of 4-week periods. Most patients were given a diet of 1,000 calories a day. There was a significantly greater increase in weight loss with chlorphentermine than with the placebo. The patients on the placebo found it difficult to keep to the restricted diet. Dryness of the mouth occurred more often in the chlorphentermine-treated patients than in the placebo group but no serious side effects were observed. The amount of weight loss

compares favorably with that reported with amphetamine and other amphetamine derivatives.

Department of Endocrinology
Guy's Hospital
London, England

- 2171** Ling, T. M. & Buckman, J. **The treatment of anxiety with lysergic acid and methyl phenidate.** Practitioner, 191:201-204, 1963.

The case of a 47-year-old Scottish woman, treated with LSD and methylphenidate for frequency of micturition, generalized anxiety, and sexual frigidity, is reported. After three treatments, (50µg LSD i.m. + 20 mg of methylphenidate i.v., 50µg LSD i.m. + 30 mg methylphenidate + 10 mg methylphenidate i.v., and 75µg LSD i.m. + 30 mg methylphenidate + 10 mg methylphenidate i.v.) and five interviews, the patient's problems were completely relieved.

Marlborough Day Hospital
London, England

- 2172** Johnston, J. D., Satchell, R. H., Shute, F. S. W., Shute, S. G. A., & Williams, G. **A long-acting trifluoperazine/amylobarbitone capsule in general practice.** Practitioner, 190:247-249, 1963.

The results of an experiment in which a time-extended capsule combining trifluoperazine (1 mg) with amylobarbitone (64 mg) was used to treat 41 patients with neurosis, mild psychoneuroses, and anxiety states, are reported. The subjects, 32 women (average age 45 years) and 9 men (average age 44 years), were given 1 capsule b.i.d. With one exception, this was continued throughout the experiment. The findings were that 26 patients responded favorably and were definitely benefitted. Side effects were minimal, consisting of one case of barbiturate allergy and one of slight drowsiness. It was concluded that this combination is suitable for the treatment of mildly, acutely, or chronically disturbed patients and is particularly indicated in anxiety and tension states.

St. Alban's Hospital
Hertfordshire, England

- 2173** Meclozine and pyridoxine in pregnancy sickness. Practitioner, 190:251-253, 1963.

A double-blind study was made of the effects of meclizine and pyridoxine in pregnancy sickness in 76 women (21 to 30 years of age). The majority of patients had not been treated previously. The results were assessed at intervals of 1 and 3 weeks. There was no significant difference in effectiveness between the two drugs, but the slightly lower level of side effects with pyridoxine makes it more preferable, providing no harmful effects on the fetus are detected in future work. The most important side effects were sleepiness and tiredness.

(No address)

- 2174** Pooley, Joan M. & Shersby, Barbara J. **A new idea and a new way with an old treatment.** Practitioner, 190:494-498, 1963.

Treatment of enuretic children over a 2-year period with an amphetamine drug, especially a long-acting, resin-bonded preparation, dexamphetamine, is discussed. It was found that 55% of the children going to the clinic had prolonged sleeping habits, and a great many of these deep sleepers were in prewaking enuretic groups. In these patients, voiding occurred just prior to the natural awaking time. The study is based on the treatment of 157 children 3 to 15 years of age, and consisting of more boys than girls. Sixty children received the resin-bonded dexamphetamine (5 mg at bedtime), and 28 received dexamphetamine sulfate (5 mg at bedtime). The children receiving dexamphetamine sulfate were given a second dose during the night and were taken to the bathroom. The long-acting dexamphetamine produced marked improvement in 75% and plain dexamphetamine helped 64% of the children treated. There were very few side effects, which consisted mainly of occasional nightmares, insomnia, or daytime irritability.

Ilford Health Area
Essex, England

- 2175** Cuthbert, K. J. R. **A clinical comparison of two hypnotics.** Practitioner, 190:509-510, 1963.

Results are reported of a clinical trial comparing two hypnotics—ethchlorvynol and glutethimide—in 47 female prisoners.

CLINICAL STUDIES 2176-2179

Ethchlorvynol (500 and 200 mg) had a hypnotic effect comparable to that of glutethimide (500 and 250 mg) in duration and quality of sleep, but with fewer side effects. Most patients preferred ethchlorvynol at the larger dose, but in some patients, the smaller dose would have been adequate.

Paddington General Hospital
Paddington, London, England

- 2176 Flint, K. N. **The use of nialamide in the treatment of psoriasis.** Practitioner, 191:354-355, 1963.

The use of nialamide in the treatment of psoriasis was investigated in 24 patients for an average period of 17.4 months (range 2 to 33 months). The effect of nialamide (75 mg/day) was evaluated by recording any change in the number and size of lesions and by noting any mental changes or variations in the patients' approach to their condition. An improvement in the number and size of lesions was observed in 15 of the patients during the first few weeks of therapy, but the improvement was not maintained for a period of longer than 6 months. It was concluded that, due to its antidepressant effect, the use of this MAO inhibitor is of temporary value in the treatment of some patients with psoriasis.

Nottingham Dermatological Clinic
Nottingham, England

- 2177 Gallant, D. M., Bishop, M. P., & Schuchs, V. **A clinical trial of an oral hypoglycemic agent in chronic schizophrenic patients.** Current Therapeutic Research, 5(12):628-629, 1963.

In a controlled double-blind study, the effects of phenformin were contrasted with the effects of placebo and chlorpromazine in a group of chronic schizophrenic patients who had received no medication for at least 60 days. The 30 subjects were divided into 3 groups and were studied for 12 weeks with maximum dosages of chlorpromazine (800 mg/day with sugar), or placebo. None of the rating measures demonstrated clinical improvement in the patients who received either placebo or phenformin, whereas 4 of 10 patients on chlorpromazine showed moderate to pronounced improvement.

Department of Psychiatry and Neurology
Tulane University School of Medicine
New Orleans, Louisiana

- 2178 Gallant, D. M., Bishop, M. P., & Steele, C. A. **A controlled evaluation of trimethoxycinnamamide.** Current Therapeutic Research, 5(11):598-599, 1963.

The therapeutic effects of trimethoxycinnamamide (maximum dosage, 1,200 mg/day) were investigated in a double-blind study using 42 male and female chronic schizophrenics. The subjects were divided into three groups and followed for 10 weeks. One group received trimethoxycinnamamide (1,200 mg/day); the second group received chlorpromazine (1,200 mg/day); and the third group received a placebo. The Lorr Psychiatric Rating Scale, the Tulane Research Battery of psychological tests, global rating of improvement by psychiatrists, and laboratory examinations were used in the comparative evaluation. There was no therapeutic difference between the placebo and trimethoxycinnamamide groups, but five patients in the chlorpromazine group showed a definite clinical therapeutic response. Patients receiving trimethoxycinnamamide showed significant weight loss during the 10 weeks.

Tulane University
School of Medicine
New Orleans, Louisiana

- 2179 Greenfield, A. R. **Control of alcoholic agitation and depression.** Current Therapeutic Research, 5(11):597, 1963.

Twenty-seven alcoholic patients (17 men and 10 women) were treated with a combination of 4 mg of perphenazine and 25 mg of amitriptyline q.i.d. for 2 to 30 days. Eleven of the patients received 5 mg perphenazine i.m. initially, and nine others received the same amount for 2 to 4 days. Elevated blood pressure, hepatic insufficiency, Laennec's cirrhosis, and gastritis were present in the group. This drug combination controlled agitation, and there was noticeable diminution of tremulousness and overt anxiety. The depression of withdrawal was also controlled.

1029 Vermont Avenue
Washington, D.C.

2180 Gallant, D. M., Bishop, M. P., Timmons, E., & Steele, C. A. A controlled evaluation of trifluoperidol: A new potent psychopharmacologic agent. Current Therapeutic Research, 5(9):463-471, 1963.

Trifluoperidol, a butyrophenone derivative, was contrasted under double-blind conditions with chlorpromazine on 36 chronic schizophrenic patients. All 36 patients, who received no medication for at least 60 days, were given either chlorpromazine (11 women and 17 men, mean age 39.5 years) or trifluoperidol (11 women and 7 men, mean age 39.0 years) for a period of 10 weeks. The daily dosage schedule for trifluoperidol was as follows: week 1, 1 mg; week 2, 2 mg; week 3, 3 mg; week 4, 4 mg; weeks 5 through 10, 6 mg. The daily dosage schedule for chlorpromazine was as follows: week 1, 200 mg; week 2, 400 mg; week 3, 600 mg; week 4, 800 mg; weeks 5 through 10, 1,200 mg. The pooled global ratings of improvement indicated significant improvement for 7 of the chlorpromazine patients as compared with 14 of the trifluoperidol patients. Correlation between these ratings and psychologic tests was excellent. There was a relative lack of hypotensive and side effects. It was concluded that trifluoperidol had a significantly greater therapeutic effect.

Tulane University
School of Medicine
New Orleans, Louisiana

2181 Sweeney, Ralph E. Oral treatment of skeletal muscle spasm: A double-blind clinical study. Current Therapeutic Research, 5(6):305-309, 1963.

A double-blind evaluation of oral therapy with combined orphenadrine-fluphenazine was carried out in patients with painful spasm or stiffness of striated muscle due to acute and chronic musculoskeletal disorders. Eighty-five patients (12 to 67 years of age) were treated in a random manner with a tablet preparation containing orphenadrine citrate (100 mg) and fluphenazine 2 HCl (0.5 mg), or with a tablet preparation of identical appearance containing only orphenadrine (100 mg). After 5 days of treatment, the effectiveness of medication was judged in terms of the degree of improvement in symptoms and signs of skeletal muscle spasm. Clinically satisfactory results characterized by moderate or marked-to-complete relief, were noted in 80% of the test group (50 patients), but in only 48% of the control group (35 patients). Mild nausea occurred

in seven patients treated with the control drug, but did not occur in any of the group treated with the combination drug.

550 Chilton Street
Elizabeth, New Jersey

2182 Shubin, Harry & Steinberg, Nathan. A study of a new tranquilizer in general practice: Emylcamate in 400 patients. Current Therapeutic Research, 5(10):527-533, 1963.

Emylcamate, a new tranquilizer was evaluated, and its behavioral toxicity was compared with that of meprobamate in 400 patients. The patient group, divided into psychoneurotics (324) and psychotics (76), consisted of 288 females and 112 males; 264 were colored and 136 were white; the age range was 6 to 79 years. Emylcamate was given in doses of 200 mg t.i.d. or q.i.d., with the maximum dosage being 2,400 mg/day. Meprobamate was given in a dose of 400 mg t.i.d. or q.i.d. The observation period varied from 2 weeks to 12 months. Emylcamate elicited an excellent result in 76 psychoneurotics and a good response in 158. Only 64% of the 100 psychoneurotics receiving meprobamate experienced significant improvement. Neither of the two medications produced encouraging effects in the psychotic patients; only 2 of 29 subjects given emylcamate showed improvement and only 1 of 10 subjects given meprobamate improved. Except for gastrointestinal irritation in 5% and drowsiness in 3%, there were no side reactions. It was concluded that emylcamate is an effective drug for the treatment of anxiety states, the clinical responses being superior to those following the administration of meprobamate.

Wolffe Hospital
Philadelphia, Pennsylvania

2183 Heather, Arthur J. An evaluation of an orphenadrine-fluphenazine combination as an antispastic and muscle relaxant. Current Therapeutic Research, 5(7):376-381, 1963.

○ Fifteen patients, with neurogenic spasticity as a complication of their illness, were studied to determine the effectiveness of an orphenadrine-fluphenazine combination as an antispastic. The muscle-relaxant properties of the preparation were evaluated in 69 patients, 11 (15.9%) of whom were withdrawn

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from the study because of side effects of the drug. The neurogenic disorders were as follows: multiple sclerosis, 5 patients; spastic paraplegia, 8 patients; quadriplegia, 1 patient; and generalized spasticity due to a bony bridge at the seventh cervical vertebra producing anterior cord pressure, 1 patient. The neurogenic spasticity was measured by applying a stimulus to the Achilles tendon, which resulted in plantar flexion that transmits gastrocnemius muscle force to a strain gage. The patients were given one orphenadrine--fluphenazine tablet b.i.d. for 10 to 15 days, and when no further decrease in spasticity was observed, the placebo was substituted without the patient's knowledge. Only 4 of the 15 patients exhibited clinical improvement, whereas the combination appeared to be outstanding as a muscle relaxant. The side effects consisted of nausea, nervousness, and dizziness.

The Eugene DuPont Memorial Hospital
Wilmington, Delaware

- 2184** Kris, Else B. **Five-year community follow-up of patients discharged from a mental hospital.** Current Therapeutic Research, 5(9):451-462, 1963.

Three groups of 100 patients each, released from mental hospitals in 3 consecutive years, were followed after discharge from the hospital for a total of 5 years. All of the patients were equal in age (average age, 35 to 40 years), sex (25% male), education (117 at elementary school level, 159 at high school level, and 24 at college level), and diagnoses (80% schizophrenics). The subjects consisted of the same percentage of acute (those hospitalized continuously for up to 2 years) and chronic patients, identified, respectively, in this report as Group A (46%) and Group B (54%). As patients showed recurrence of psychotic symptoms, drug therapy was reinstituted. A larger percentage of Group B patients (86%) needed maintenance therapy than did Group A patients (60%). When both groups were on medication, their chances of remaining unhospitalized were equal. The average daily dose of chlorpromazine (50 to 150 mg) was the same in both groups. One-third of the patients received medication at bedtime only, one-half were on a b.i.d. dose, and one-sixth received no medication. The rehospitalization rate for both groups was the same. After 5 years of observation, 63% of the 300 patients were still in the community, and 40% of these were fully self-supporting. Those subjects employed showed good job stability and had the lowest hospitalization rate. Those subjects living alone and those

sharing a household during the first 2 years of observation had the same 5-year rehospitalization rate.

New York State
Department of Mental Hygiene
New York, New York

- 2185** Muniz, Herminio, Zug, Charles K., & Pitt, Leldon P. **Thiethylperazine for the prevention of postoperative nausea and vomiting.** Current Therapeutic Research, 5(7):356-359, 1963.

Clinical evaluation of thiethylperazine in preventing or reducing postoperative nausea and vomiting was carried out in which the drug was compared with a control series, and a double-blind comparison was made with placebo. Thiethylperazine, 10 mg, was administered by tablet or i.m. injection before surgery and twice following surgery in 299 patients. Another group of 139 patients received no antiemetic and served as controls. A followup study utilizing a double-blind procedure with placebo was investigated with 85 patients receiving 10 mg of the drug p.o. or a 2 cc ampule (5 mg/cc) and with 86 receiving the placebo. Twenty mg or 4 cc were administered prior to and following surgery. In the patients receiving thiethylperazine, there was 59.6% less nausea and/or vomiting than in the controls. With patients receiving the double dose, there was 55.0% less overall vomiting, with the most significant reduction occurring in the vomiting rated as severe. The side effects noted were drowsiness and hypotension. There was no evidence of any delay in recovery of alertness in either series of patients.

811 Spruce Street
Philadelphia, Pennsylvania

- 2186** Geert-Jorgensen, Einar. **Treatment of anxiety neuroses and psychosomatic syndromes using a new Librium-metabolite, RO 4-5360.** Acta Psychiatrica Scandinavica, 39:209-217, 1963.

A new chlordiazepoxide metabolite, RO 4-5360, was tested in a total of 146 cases. In 58 unhospitalized cases (34 females and 24 males) given an initial dose of 10 mg q.i.d., which was reduced to 5 mg q.i.d. or t.i.d. + 10 mg at bedtime, RO 4-5360 produced a better response in anxiety and organ neuroses. In 88 hospitalized cases (25 males and 63 females), the effect of the drug was

again most satisfactory in cases of anxiety and psychosomatic neuroses, but unsatisfactory in obsessive-compulsive neuroses. The sedative effect of RO 4-5360 was excellent in cases of endogenous mental depressions but did not possess a specific, antidepressant action. Side effects were few, and, in a few cases, treatment was discontinued because of the development of severe symptoms of fatigue and dizziness. The action of RO 4-5360 seemed superior to that of chlorthalidoxepoxide; however, in identical doses side effects of RO 4-5360 were more severe than the effects of chlorthalidoxepoxide.

Frederiksberg Hospital
Copenhagen, Denmark

- 2187 Svendsen, B. Borup & Willadsen, J.
The use of haloperidol (Serenase) in chlorprothixene resistant patients. *Acta Psychiatrica Scandinavica*, 39:351-355, 1963.

A retrograde evaluation has been made of the results from case histories and from the authors' personal knowledge of chlorprothixene resistant patients who were given haloperidol. Haloperidol (3.0 to 30.0 mg/day was given to 38 patients (15 to 60 years of age) who had previously received chlorprothixene (up to 800 mg/day for at least 1 month). Three manic patients and two patients with psychogenic psychoses were cured. One of the nine manic patients showed no effect with haloperidol. Fifteen of the 24 schizophrenic patients showed good to moderate improvement. Side effects (restlessness, physical distress, parkinsonism) were more disturbing to the patients than those effects occurring with phenothiazine therapy, but the effects were not serious. It was concluded that haloperidol should be considered for the treatment of patients in whom the phenothiazines have failed.

Rigshospitalet, Psychiatric Clinic
Copenhagen, Denmark

- 2188 Lochner, Karl H., Scheuing, Marilyn R., & Flach, Frederic F. **The effect of L-triiodothyronine on chronic schizophrenic patients.** *Acta Psychiatrica Scandinavica*, 39(3):413-426, 1963.

Following a review of the various concepts and results of investigations concerning the possible relationships between thyroid hormones and schizophrenia, a description was

given of an investigation of the clinical effects of L-triiodothyronine on 30 apathetic, chronic schizophrenic male patients. The patients, 30 to 45 years of age with no endocrine dysfunctions, were given 50 µg b.i.d. of L-triiodothyronine p.o. (15 patients), which was doubled in 1 week to 200 µg/day for 6 weeks, or placebo (15 patients). The drug was administered under double-blind conditions. Twelve patients showed changes while receiving L-triiodothyronine, of which seven responded with increased motor activity, sociability, interest in the environment, and improved performance at work; the remaining five manifested behavior of a more disturbed character. Of the two patients who changed while receiving placebo, one responded with restlessness, exhilaration, overtalkativeness, sociability, and cooperativeness. The other became restless, irritable, and negativistic. The reasons for such variability in responses were not clear, even after a review of the case histories.

Franklin Delano Roosevelt Hospital
Montrose, New York

- 2189 Bjorn, S. & Rasmussen, Carlo.
Sordinol (clopenthixol) in the treatment of schizophrenics. *Acta Psychiatrica Scandinavica*, 39(3):427-436, 1963.

Clopenthixol was used in the treatment of 70 female schizophrenic patients, who were classified as hebephrenics, catatonics, or paranoics. The average duration of psychoses was 24.4 years, and the average age was 52.1 years. Three dosage schedules were followed: (1) 10 mg t.i.d. increased by 10 mg every other day administered in old, frail patients and in patients with mild heart disease; (2) initially, 25 mg t.i.d., increased by 25 mg every 3 days to 16 patients; and (3) 10 mg t.i.d. increased by 10 mg every 5 to 12 days in 4 patients who had shown severe side effects on other psychotropic drugs. On all dosage schedules, the dose was increased to 300 or 450 mg daily, depending on the response and side effects manifested. Twenty-three of the 70 patients obtained lasting benefit, and 13 had to discontinue the drug because of side effects. The lobotomized patients gave equally as good response to clopenthixol as did the nonlobotomized ones. The maximum effect was observed in the age range of 40 to 50 years, in nondemented patients, patients with a short duration of psychosis, and among paranoic patients. Parkinsonism was observed in about 70% of the patients. An

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increase in transaminase and phosphatase values was observed in 33 cases. The EEG tracings were altered in 11 of 12 cases. Difficulties in adjusting the dosage are stressed. This drug should be used only for inpatients and for patients on controlled aftertreatment.

State Hospital
Nykobing Sjaelland, Denmark

2190 Gottfries, C. G. Clinical trail with the monoamino oxidase inhibitor **tranlycypromine** on a psychiatric clientele. *Acta Psychiatrica Scandinavica*, 39(3):463-472, 1963.

A pilot study, followed by a double-blind study, of the effects of tranlycypromine in depressive patients is discussed. In the pilot study, one-half of the 32 patients receiving 15 to 30 mg of tranlycypromine daily for 2 to 6 weeks appeared to be favorably affected by the drug. The side effects were dizziness and a feeling of faintness. Headache and hemiplegia observed in one patient may have been a side effect of the drug. There was no clear-cut evidence of liver damage, as ascertained by SGPT and SGOT determinations. The urinary tryptamine was increased, which indicated MAO inhibition. Fifty depressive patients were studied in the double-blind tests. One group was made up of endogenous depressive patients, and the other group was made up of all other types of depression. They were treated with 30 mg/day of tranlycypromine or placebo. A positive effect was demonstrated in 6 of the 25 patients receiving the drug against 2 of the 25 receiving the placebo. Dizziness again was the most common side effect. There was no increase in the SGPT in the drug-treated group, but an increase was noted in two of the patients in the placebo group.

Department of Psychiatry
General Hospital of Malmö
Malmö, Sweden

2191 Phillips, Fred J. **Peptic ulcer: Treatment with a combination of meprobamate and tridihexethyl chloride.** *Clinical Medicine*, 70(7):1303-1306, 1963.

A discussion is presented of the response of 66 (20 females and 46 males) peptic ulcer patients treated with a combination tablet of meprobamate 400 mg and tridihexethyl chloride 25 mg administered in various dosages, depending on the individual patient

requirement, and followed closely up to 4 years. As their symptoms improved, or as new complaints arose, the management was altered appropriately. When indicated, X-ray studies were done. Excellent results (no disabling ulcer symptoms with intermittent use of the medication) were obtained in 74%; satisfactory results (recurrence of ulcer symptoms but satisfactory remission with the medication) were found in 20%; and unsatisfactory results (recurrence of ulcer, producing time loss, hospitalization, or surgery) occurred in 6%.

Quakertown, Pennsylvania

2192 Ort, Frederick. **Adjuvant treatment of obesity with an anorecticcaloric agent.** *Clinical Medicine*, 70(11):1999-2006, 1963.

Psychological counseling, dietary control, and anorectic drugs were used in the treatment of 50 obese patients (42 females, 8 males; 16 to 64 years of age). Exogenous obesity was the primary diagnosis in 39 of the patients. They were treated for an average of 8 weeks. A timed release tablet containing amobarbital 60 mg, methamphetamine hydrochloride 10 mg, and thyroid 150 mg was given before breakfast. Gradual weight loss was experienced by 49 of the 50 patients; 38 patients obtained a superior result; 11 others showed good to fair results; and one patient did not benefit from the medication. Side effects were infrequent, mild, and transitory and did not interfere with therapy. Twenty-eight percent of the patients experienced blood pressure reduction along with weight loss, but there was no instance of substained blood-pressure elevation.

Quakertown, Pennsylvania

2193 Mulla, Nejdat P. **Evaluation of trimethobenzamide with pyridoxine in nausea and vomiting of pregnancy.** *Clinical Medicine*, 70(11):2052-2054, 1963.

A double-blind study of the antiemetic effects of trimethobenzamide and pyridoxine and of meclizine and pyridoxine was performed on 200 women during the first trimester of pregnancy. Half of the women received one drug combination and half were given the other combination. Of the 100 patients treated with meclizine and pyridoxine, 71 had excellent or good results, and 29 had fair to poor results.

Twelve patients, who had previously received this combination with good results, did not respond and had to be given another preparation. Of the 100 patients treated with trimethobenzamide and pyridoxine, 90 showed excellent to good results.

Kent, Ohio

- 2194 Cromwell, Henry A. **Controlled evaluation of psychotherapeutic drug in internal medicine.** Clinical Medicine, 70(12):2239-2244, 1963.

A controlled, double-blind study that compares the effects of placebo with diazepam (2 to 5 mg, two to four times daily) in 31 patients (13 men and 18 women) with organic and functional disorders is presented. All the patients were extremely tense and anxious with depressive features of varying intensity, and three patients were also psychotic. The medications were administered for 1- to 2-week periods. All patients received both placebo and diazepam. Supportive psychotherapy was maintained throughout. There was marked to moderate improvement in 30 patients receiving diazepam and in only 1 receiving the placebo. The order in which the two agents were administered did not affect the response. There was marked improvement in neurotic symptoms, with less depression among the subjects. Side effects included nightmares and drowsiness, but these were not significant.

Houston, Texas

- 2195 King, Arthur. **Phenelzine treatment of Roth's calamity syndrome.** Medical Journal of Australia, 1:879-883, 1962.

A study was made to determine the effect of phenelzine in the treatment of Roth's calamity syndrome. Twenty-eight patients (23 females and 5 males, 23 to 66 years of age) were treated with phenelzine and followed up for a period ranging from 2 to 9 months. All of the patients had been ill for periods ranging from 5 months to 30 years with previous psychiatric treatment, including ECT and tranquilizer medication. The patients were treated as outpatients, were given 15 mg of phenelzine t.i.d. beginning at the time of diagnosis of the syndrome, and were reviewed monthly. Side effects observed included postural hypotension, bradycardia, postprandial dyspepsia,

and weight gain. Twenty-five patients (89.4%) reported complete relief of depersonalization after 4 weeks. Twenty-two (88%) of the 25 patients who completed 3 months of treatment reported complete relief from experiences of unreality. Twenty-one patients (75%) had noticeable improvement in their phobic aversions after 1 month, and after 3 months, amelioration had occurred in 21 cases. Depersonalization was the first symptom to fade. Secondary features then began to diminish in intensity, so that after 1 month, 17 patients (60.7%) of the 28 reported themselves improved, and after 3 months 18 out of 21 were improved.

Mont Park Hospital
Victoria, Australia

- 2196 Chesher, G. B. **An evaluation of tranlycypromine ("Parnate") in the treatment of depression.** Medical Journal of Australia, 1:949, 1962. (Letter).

This response to a paper on the use of tranlycypromine in depression (May 5, 1962 issue) expressed some doubt over the interpretation of the data by the author because of the use of the same patients in several subdivisions. It would appear that the numbers upon which the original conclusions were based were inadequate.

20 Macleay Street
Potts Point
New South Wales, Australia

- 2197 Brattemo, Carl-Erik & Lassenius, Borje. **Lysergsyrdietylamid en klinisk och psykologisk studie. (Lysergic acid diethylamide, a clinical and psychological study.)** Nordisk Medicin, 69:193-197, 1963.

A clinical and psychological study of the effects of LSD was made in 7 female and 6 male subjects (10 normals and 3 psychoneurotics). A brief review is given of the pharmacology, psychological effects, and therapeutic uses of LSD, and some results of earlier psychological studies are mentioned. The effects of LSD were measured by performance on several psychomotor and perceptual tests, a self-rating scale, and a Swedish proverbs test. The LSD was given in doses of 75µg to 100µg s.c. The LSD-treated subjects experienced depersonalization, and their functions were greatly impaired in tasks requiring verbal and

perceptual fluency, perceptual analyzing, and synthesizing ability. Psychomotor activity was uncoordinated and the subjects gave illogical responses. Their reactions approximated those seen in a group of schizophrenics studied earlier. These results provided evidence supporting the hypothesis that LSD causes primitivization of certain psychic functions.

Sidsjöns Hospital
Sundsvall, Sweden

- 2198 Odegard, Ornulv. **Utskrivningsmonstret fra norske psykiatriske sykehus for og etter den moderne medikamentbehandling.** (Pattern of discharge from Norwegian mental hospitals before and after the introduction of modern drugs.) Nordisk Medicin, 70:961-965, 1963.

A comparison was made of the pattern of discharge and readmission from Norwegian mental hospitals before and after the introduction of psychotherapeutic drugs. Patients admitted for the first time between 1955 and 1959 were followed up until the end of 1960. Statistics were compared with predrug patients admitted from 1948 to 1952 and followed up until 1953. A total of 8,675 predrug patients (6,315 functional psychoses and 2,360 with other psychoses) and 9,792 drug patients (7,000 functional psychoses and 2,792 with other psychoses) was studied. Statistics on the duration of hospital stay showed that in the predrug era 112.0 functional psychotics and 121.2 with other psychoses per 1,000 admissions were hospitalized for 1 month or less, whereas 145.0 functional psychotics and 126.7 with other psychoses per 1,000 were kept for 1 month or less during drug treatment; 175.4 and 117.8 per 1,000 were kept for 2 to 3 months as compared to 186.1 and 98.0 per 1,000 for the drug patients; 6.9 and 2.4 per 1,000 were kept 2 to 5 years in the predrug period as compared to 10.4 and 3.3 per 1,000 in the drug era. With drug treatment, a very slight increase in discharge rates and a tendency toward a shorter hospital stay existed. It is shown, however, that a great improvement in therapeutic results occurred between 1936 and 1950. The unemployment problem since 1945 may have exerted a detrimental effect on the rehabilitation of psychiatric patients.

Gaustad Hospital
Oslo, Norway

- 2199 Bratfos, Ole & Retterstol, Nils. **Et kontrollert klinisk forsok metaminodiazepoxid.** (A controlled clinical study of chlordiazepoxide.) Nordisk Medicin, 70(12): 1015-1017, 1963.

The effects of chlordiazepoxide were studied in 61 neurotic patients chosen from a group of 350 patients as being likely to respond to therapy with this drug. The patients, 33 females and 28 males, ranged in age from 15 to 64 years, with an average of 33 years. Each of the 61 patients was given either chlordiazepoxide or placebo for 1 week and the alternate preparations the following week. The effects on anxiety, tension, restlessness, irritability, depression, compulsiveness, conversion and neurasthenic symptoms, headache, anorexia, and sleep disturbances were compared. Chlordiazepoxide had a slightly better effect on anxiety and sleep disturbances than placebo, but was no more effective than placebo in relieving the other symptoms.

University Psychiatric Clinic
Oslo, Norway

- 2200 Idestrom, Carl-Magnus, Kahan, Elisabeth, & Molander, Lars. **Feniprazine—en efterundersokning. (Pheniprazine—a follow-up study.)** Nordisk Medicin, 70:1188-1193, 1963.

Results of a followup study of 122 patients who had completed a course of pheniprazine treatment 6 months earlier are reported. A comparison of the results immediately after termination of treatment and of the patient's opinions of the treatment at least 6 months later showed almost complete agreement. Most of the patients had previously received treatment with other psychotropic drugs with no success. Data derived from a modification of the personality-factor questionnaire of Cattell et al., which was completed by each patient, are discussed in detail. It was concluded that, although pheniprazine causes severe side effects in some cases, there is a definite therapeutic need for the drug, and it should be used until a less toxic drug can be found that produces comparable therapeutic effects.

Charles Hospital
Stockholm, Sweden

- 2201 Astrup, C. & Aslanov, Anatolif G.
Experimental studies of psychotropic drugs in schizophrenics. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 316-320. (Psychopharmacological methods.)

Schizophrenic patients tend to reveal inhibition of unconditioned reflexes. The effects of psychotropic drugs on unconditioned reflexes in several subgroups of schizophrenics were investigated. The drugs used were chlorprothixene (100 mg), imipramine (75 mg), tetrabenazine (50 mg), prochlorperazine (50 and 75 mg), chlorpromazine (50 and 100 mg), and isocarboxazid (20 mg). Electric stimulation was given by the Du Bois-Reymond inductor. The unconditioned responses tended to be inhibited by all drugs. It was found that the inhibitory effects of drugs become more marked during the treatment process than during studies of single doses. Chlorprothixene gave the sharpest inhibitory effect. The inhibitory effect varies with the clinical condition. It is more marked in severe catatonic and mild paranoid defects than it is in severe paranoid and hebephrenic defects.

Gaustad Hospital
 Oslo, Norway

- 2202 Ruttkay-Nedecký, I. & Kellerová, E.
A clinical testing procedure for the evaluation of the after-effect of reserpine and amine oxidase inhibitors. Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 326-329. (Psychopharmacological methods.)

A clinical testing procedure for detecting the specific action of reserpine or monoamine oxidase inhibitors is described. The single deep-breath-induced vasoconstriction in acral skin regions is an adrenergic reflex sensitive to small doses of reserpine (0.50 mg p.o.) in three normotensive subjects. A total dose of 1.75 mg of reserpine significantly depressed the vasoconstrictor reflex, notwithstanding the duration of the time intervals between the single deep inspirations that are used for eliciting the vascular response. The depression of the reflex continues for various time intervals after

withdrawal of the drug. Consequently, the testing procedure gives no information about the actual reserpine blood level, but rather, demonstrates reserpine-induced changes in adrenergic vascular structures. A mixture of 4.2 g of bromide and 0.35 g of phenobarbital or chlorpromazine 50 mg for 7 days had no reserpine-like depressive action on the reflex. The premedication with a monoamine oxidase inhibitor, isocarboxazid (30 mg/day for 7 or 21 days), had an antagonizing action on the inhibitory effect of reserpine, which continued for various periods after withdrawal.

Institute of Experimental Medicine of Slovak Academy of Sciences
 Bratislava, Czechoslovakia

- 2203 Toscano Aguilar, M. La **psilocybine: Perspectives d'utilisation en psychiatrie clinique. Psilocybin: Possibilities in clinical psychiatry.** Acta Neurologica et Psychiatrica Belgica, 63:114-131, 1963.

Possible clinical uses of psilocybin are discussed, based on the use of this drug in 35 hospitalized mental patients—27 males and 8 females. According to previously published material, the therapeutic effect of psilocybin is exerted by two actions—a direct biological action on the organism and a psychological action on disorders of mood and awareness. The effects of small doses (0.5 mg/day) and large doses (10 to 16 mg/day) on patients are described. Somatic effects were constant, but psychic effects varied. Objective and subjective effects are described. Somatic effects were constant, but psychic effects varied. Objective and subjective effects are discussed. The selection and preparation of patients for psilocybin therapy and the role of the therapist to the patient under psilocybin are described. Psilocybin may prove useful in treating juvenile delinquents.

43 Avenue Jacques Pasteur
 Brussels, Belgium

- 2204 Katila, O. & Pihkanen, T. **Observations on the use of haloanisone in the treatment of certain psychiatric diseases and organic psychosyndromes.** Acta Neurologica et Psychiatrica Belgica, 63:291-297, 1963.

In order to evaluate the therapeutic effects of haloanisone (15 to 60 mg/day) on a variety of organic psychosyndromes

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and psychiatric disease, 35 patients (17 to 91 years of age) with a variety of diagnoses were studied. The results indicated that haloanisone was useful in the treatment of psychotic symptoms, particularly in states of confusion and agitation connected with cerebrovascular disease. In nine schizophrenic patients, four responded favorably. There was a low incidence of side effects, and none were severe.

Second Department of Hesperia Hospital
Helsinki, Finland

- 2205 Lopez-Pinto, C., Fosati, P., Galibert, P., & Delandtsheer, J. M. L'acetazolamide (Diamox) dans les suites immédiates des traumatismes crâniocérébraux. (Application of acetazolamide (Diamox) in the immediate consequences of craniocerebral trauma.) Acta Neurologica et Psychiatrica Belgica, 63(5):298-314, 1963.

Acetazolamide given i.v. in doses of 500 mg t.i.d. combined with one or two injections of 60 ml hypertonic glucose serum was used to treat posttraumatic intracranial hypertension in 62 patients, 14 to 71 years of age. The treatment was successful in 54 cases. The drug enhanced cerebral circulation and decreased cerebrospinal fluid secretion. Diagnosis and outcome are described briefly for each patient. The activity of acetazolamide appears to depend on inhibition of carboanhydrase and is independent of renal activity.

University of Lille Medical School
Lille, France

- 2206 Schunzelaar, K. Treatment of enuresis and encopresis with Tofranil in chronic psychiatric female inpatients. Acta Neurologica et Psychiatrica Belgica, 63:333-336, 1963.

Imipramine (50 to 100 mg) was given to chronic psychiatric female patients, with diagnoses of mental deficiency, manic reactions, depressive reactions, and demential state, in order to study the drug's effects on enuresis and encopresis in these patients. The ages of the patients varied between 34 and 86 years. The results showed that imipramine caused a significant improvement in incontinence. The side effects observed were urinary retention, agitation, dryness of mouth, tachycardia, perspiration, and tremor. Imipramine

should be given in low doses when used in the treatment of elderly arteriosclerotic patients.

(No address)

- 2207 Bobon, J., Collard, J., & Lecoq, R. Benpéridol et promazine: Une étude comparative double blind en gériatrie mentale. (Benperidol and promazine: A double-blind comparative study in geriatric medicine with special emphasis on senile mental changes.) Acta Neurologica et Psychiatrica Belgica, 63(10):839-843, 1963.

The sedative effect of benperidol, a butyrophenone derivative related to haloperidol, was compared with that of promazine in 15 patients (61 to 95 years of age) with agitation resulting from senile dementia. A double-blind testing procedure and a nominal score system for evaluating clinical symptomatology and pharmacological effectiveness were used. The optimum daily oral doses were found to be 60 mg for promazine and 2.85 for benperidol; maximum doses were 90 mg and 4.5 mg, respectively. The average duration of treatment was 3 months. Benperidol was more effective in inhibiting psychomotor excitation, verbal excitation, and disorders of mood, with the exception of senile euphoria. Promazine was more effective against insomnia and confabulation. Both drugs were well tolerated, but benperidol caused drowsiness in therapeutic doses.

Psychiatric Clinic
University of Liege
Liege, Belgium

- 2208 Bobon, J., Collard, J., & Daigneux-Delhez, R. Etude psychopharmacologique d'un dérivé méthylé du halopéridol: Le méthylpéridol ou R 1658 (9^e butyrophénone). (Psychopharmacological study of a methyl derivative of haloperidol: Methylperidol, or R 1658 (the 9th butyrophenone).) Acta Neurologica et Psychiatrica Belgica, 63(10):839-843, 1963.

Methylperidol, a neuroleptic of the butyrophenone series, was tested in 20 chronic psychotic patients. Diagnoses of these patients included paranoid schizophrenia in 8 cases, schizoid in 1, superimposed hebephrenia in 3, paraphrenia in 2, paranoia in 3, general paralysis in 1, manic state in 1, and chronic involutional depression in 1. Patients ranged in age

from 28 to 74 years, with an average of 52 years. Average duration of illness was 16.5 years, and average duration of current hospitalization was 116 months. The initial dose of methylperidol was 1 to 20 mg/day p.o., and the maximum dose was 72 mg/day p.o. Average optimum dose was 18 mg/day p.o. Duration of treatment ranged from 6 to 120 days, with an average of 66 days. Statistical analysis showed that the antipsychotic potency of methylperidol was moderate compared with that of haloperidol. Extrapyramidal effects were also less frequent. Methylperidol caused vomiting in two patients and dyspnea in one.

Psychiatric Clinic
University of Liege
Liege, Belgium

- 2209 Husquinet, H. *Remarques sur l'action de l'iproniazide (Marsilid) dans les syndromes dépressifs.* (Observations on the action of iproniazid (Marsilid) in depressive syndromes.) *Acta Neurologica et Psychiatrica Belgica*, 10:902-909, 1963.

The clinical effectiveness of iproniazid is discussed, based on data derived from 20 cases, 5 hospitalized patients and 15 outpatients, that were treated with the drug. Results were excellent in three inpatients and in five outpatients. Three case histories are reported in detail. In Case 1, a 40-year-old, hospitalized, female depressive, who had received ECT previously, was given iproniazid in doses of 75 mg daily up to a maximum of 375 mg daily; dosage was decreased to 75 mg daily upon relief of symptoms. In Case 2, a 58-year-old male outpatient with chronic psychasthenic depression was given 150 mg iproniazid/day and 15 mg chlorprothixene t.i.d., with excellent results. In Case 3, a 38-year-old male outpatient, with a history of addiction to amphetamine and methamphetamine, improved and gained weight with iproniazid, but after discharge, he began taking 3 g of the drug daily. The patient showed surprisingly weak side effects in spite of the large dose.

14 rue Courtois
Liege, Belgium

- 2210 Nakazawa, T. (Clinical trial of a new nicotinic acid derivative, meso-inositol-hexanicotinate, in neuropsychiatry.) *Brain and Nerve*, 15:902-909, 1963.

The effects of a nicotinic acid derivative, meso-inositol-hexanicotinate, were studied in 36 neuropsychiatric patients. Included in this group were patients being treated for cerebrovascular diseases, neuritis, diseases involving the autonomic nervous system, posttraumatic neurosis, and spinomuscular diseases. The meso-inositol-hexanicotinate was added to the previous drug regimen of each patient, which included such compounds as thiamine and minor tranquilizers. The drug was remarkably effective in relieving symptoms of autonomic involvement, such as headache, sleeplessness, nausea, disturbances of consciousness and perception, and alterations in blood pressure. In 11 cases of arteriosclerosis, the drug lowered total serum cholesterol. Of nine cases with various neuroses, six showed marked improvement in hallucination and anxiety. The only side effects observed were a few cases of nausea and vomiting.

Keio University School of Medicine
Keio, Japan

- 2211 Funusa, W. (Clinical effects of chlordiazepoxide.) *Brain and Nerve*, 13:925-928, 1961.

The clinical results of chlordiazepoxide treatment in 58 subjects are reported. The 58 subjects were diagnosed as follows: 30 neurotics, 10 obsessive-compulsive neurotics, 11 depressives, 4 schizophrenics, and 1 case of Huntington's chorea. Chlordiazepoxide was most effective in relieving anxiety and tension. The drug was also effective in depressives and in obsessive compulsives, but showed no effect in schizophrenics or in the patient with Huntington's chorea. One elderly patient showed unstable gait, drowsiness, and hypotension on high doses of the drug. Other side effects included two cases of insomnia and two cases of dermatitis.

Niigata University School of Medicine
Niigata, Japan

2212 Espinosa, J. Erfahrungen mit chlórdiazepoxyd (Librium) bei kindern mit verhaltensstörungen. (Experiences with chlórdiazepoxide (Librium) in childhood behavioral disturbances.) In: Stur, Otto, ed. Part II. Psychological and sociological problems in imbecility drug treatment. Proceedings of the Second International Congress on Mental Retardation, Vienna, 1963, p. 131-136.

Chlórdiazepoxide was given to 40 children with behavior disorders. The patients were mostly females, 7 to 17 years of age. Treatment consisted of 15 to 30 mg/day chlórdiazepoxide, in three doses, for 2 to 4 months. Results differed, depending on the presence or absence of oligophrenia. In 11 oligophrenics without pathological EEG, the drug's effect was inconstant and only partially successful. In seven oligophrenic patients with epileptic convulsions or pathological EEG, the drug was remarkably successful, preventing grand mal, greatly reducing petit mal, and improving behavior in school. Results were encouraging in 22 nonoligophrenic patients with behavioral disorders and normal IQ. In addition to general calming, neurotic symptoms disappeared very rapidly, particularly in patients showing a latent anxiety state. Results showed that postprandial vomiting disappeared on the first day of chlórdiazepoxide administration, nocturnal fears disappeared in a few days, there was substantial improvement in three of four stutterers, asthma in one patient was cured, and nocturnal enuresis was cured in three older children, but was unchanged in 11 others. In one of two patients of this group with pronounced behavior disorder, no substantial change was observed. Tolerance was excellent, with drowsiness observed in only two patients when chlórdiazepoxide was given at high doses. Appetite and weight increased in most patients.

Alcira 15
Valencia, Spain

2213 Sylvester, P. E. A controlled cross-over trial of chlórdiazepoxide (Librium) in mental deficiency. In: Stur, Otto, ed. Part II. Psychological and sociological problems in imbecility drug treatment. Proceedings of the Second International Congress on Mental Retardation. August 14-19, 1961. Basel, Switzerland, Karger, 1963, p. 137-146.

A controlled blind, cross-over trial was conducted over a 2-month period on three groups of mentally defective patients to

test the following three possible effects that chlórdiazepoxide might have: (1) muscle-relaxant properties in spastic patients; (2) quietening effects on destructive and difficult patients; and (3) because of possible quietening effects, the ability to concentrate better and learn faster, which might follow, in a group of young, mentally subnormal boys. Group 1 consisted of 16 patients (7 males and 9 females, ranging in age from 8 to 49 years) with spastic limbs. In group 2 there were 12 severely subnormal male patients, 8 to 23 years of age. Group 3 consisted of 23 male patients, 9 to 19 years of age, capable of receiving some formal education. During the first month half of the patients were administered chlórdiazepoxide (1 mg/kg) capsules and the other half a dummy capsule containing lactose and starch. Medication was switched over for the second month of treatment. Side effects occurred in seven patients in this study (14%). Lethargy was noted in two, excessive excitability in one, aggressiveness in two, and two complained of some dizziness. One mongol boy developed erythema nodosum 6 weeks after withdrawal of chlórdiazepoxide. Chlórdiazepoxide did have a beneficial effect as a muscle-relaxant on the group of patients with spastic limbs and would appear to be a valuable therapeutic aid in the management of these cases. Chlórdiazepoxide failed to quieten destructive and difficult severely subnormal males. There was no evidence that the subnormal patients with some amount of educability were helped by the treatment.

St. Lawrence's Hospital
Caterham, Surrey, England

2214 Faure, H. & Faure, M. L. Les apports du nozinan en neuro-psychiatrie infantile (Levomépromazine, 70.44 R.P.). (Actions of Nozinan in infantile neuropsychiatry (Levomépromazine, 70.44 R.P.).) In: Stur, Otto, ed. Part II. Psychological and sociological problems in imbecility drug treatment. Proceedings of the Second International Congress on Mental Retardation. August 14-19, 1961. Basel, Switzerland, Karger, 1963. p. 160-164.

A 4-year study of RP-7044 (Nozinan) used in the treatment of 250 children, 2 to 15 years of age, demonstrated that the drug is a strong regulator of sleep patterns and is a decided aid in the maintenance of self-control. Treatment was in a clinical or hospital environment and in reeducation centers. In the greater portion of the children treated, falling asleep at night

was quickly accomplished, and they slept through the night and stayed asleep longer than usual. Administration of the drug at noon helped to establish an afternoon-nap pattern. Physiologically, RP-7044 acted as an hypnotic or parahypnotic and alleviated motor spasms and nightmares. The action of the drug on equilibrium and self-control was not only global but also of a regulatory hypnotic type. Improvements were noted in emotional stability, morbidity, anxieties, and spasms. In pre-psychotic states, as well as in epilepsy, RP-7044 demonstrated great therapeutic efficacy. The administration RP-7044 in combination with glutamic acid and/or with RP-8228 (phacetoperane) was especially beneficial. Tolerance to the drug, even over prolonged periods of medication, was exceptional. Dosages of 6 to 12 mg, 1 to 4 times/day was given to children up to 7 years of age and from 12 to 25 mg/day to those 7 to 15 years of age. Side effects were excessive wakefulness, digestive disorders, changes in red-blood cell count with leukopenia supersegmentation, and mononuclear increase, but never to a dangerous degree.

Bonneval
Eure-et-Loir, France

- 2215 Beaujard, M. *Le phacetoperane dans l'arriération mentale chez l'enfant.* (Phacetoperane in mental retardation in children.) In: Stur, Otto, ed. Part II. Psychological and sociological problems in imbecility drug treatment. Proceedings of the Second International Congress on Mental Retardation. August 14-19, 1961. Basel, Switzerland, Karger, 1963, p. 165-167.

Experiments with phacetoperane, a psychostimulant derivative of RP-7890, were conducted on 50 infants and children, 5 to 14 years of age, both males and females, with IQ's of 30 to 75 and problems of attention, apathy, and inhibitions. Psychometric control of observed clinical results and psychological research in the methods used were the focus of the study. Research was conducted in modifications of medication dosage and in combinations with neuroleptics. Results show an improvement in span of attention of several hours' duration in 27 out of 50 cases. The results of longer medication show an improvement of 2 to 6 points in the I.Q. in 21 out of 32. Tolerance to the drug and effects on behavior are affected by family situation; the emotional stability of the child; the variation of dosage; and the combined medication with sedatives or neuroleptics, such as levomepromazine for anxiety

and prochlorperazine for aggressive states. Studies with RP-7204 have confirmed the value of combined medication.

Bron
Rhône, France

- 2216 De Carvalho, Henrique Marques, Bairo, Ivo Soares, & Cavallo, Tito. *O cloridrato de 2-etilamino-3-fenil-norcanfan (H-610) por via endovenosa no tratamento das doenças mentais: Estudo clinico de 38 pacientes.* (2-Ethylamino-3-phenyl-norcanfan hydrochloride (H-610) in intravenous administration in the treatment of mental diseases: Clinical study of 38 hospitals.) *O Hospital*, 64:113-122, 1963.

The effects of 2-ethylamino-3-phenyl-norcanfan HCl (H-610) given concomitantly with vitamin C and glucose were studied in 38 psychiatric patients. The patients' diagnoses included 27 cases of depression, 7 of psychasthenia, 2 of hysteria, 1 of compulsive neurosis, and 1 of endotoxic psychosis. Initial and maximum dosage, duration of treatment, and outcome are tabulated for each patient. Of 27 depressives, complete remission was achieved in 19, and definite improvement occurred in 3. Of the seven psychasthenics, five showed improvement, but none showed complete remission. No side effects were observed.

(No address)

- 2217 De Mattos Filho, Antonio Corrêa. *Emprego de um tranqüilizador e de sua associação a um espasmolítico em pacientes obstétricas.* (Experimental study of the use of a tranquilizer and its combination with a spasmolytic in obstetric patients.) *O Hospital*, 62(3):503-508, 1963.

Chlordiazepoxide and a combination product (Librax) containing chlordiazepoxide and bromide in doses of 5 mg and 2.5 mg/capsule, respectively, were tested in 105 pregnant women for relief of neurovegetative disturbances during early pregnancy and of anxiety and tension preceding and during labor. The patients were divided into three treatment groups: Group 1, 53 cases with predominant neurovegetative disorders; Group 2, 41 cases with anxiety and tension; and Group 3, 11 cases with anxiety and irritability. Group 1 was given one capsule of Librax for 10 days or two capsules for 5 days. Group 2 was given 10 to 30 mg

CLINICAL STUDIES 2218-2220

chlordiazepoxide daily for 10 days. Group 3 was given one capsule of Librax every 2 hours from the beginning of labor. Results for each group are reported. In general, the drugs produced favorable responses, except in a small group of patients during labor. Librax probably was not properly absorbed in patients during labor. Side effects in Group 1 included dry mouth and numbness in the extremities in 12 cases and insomnia in 2, and those in Group 2 included drowsiness and anorexia in 8 and aggravation of anxiety in 7.

Alfredo Marcondes Obstetrical Hospital
São Paulo, Brazil

- 2218 Mackay, R. I., Wiseman, A. G. M., Harding, P., & Riley, M. A. Monoamine oxidase inhibitors and mental subnormality: Experiences with nialamide. *Journal of Mental Deficiency Research*, 7(2):107-121, 1963.

The effect of nialamide (50 to 75 mg/day), using a double-blind cross-over design, was studied for 4 weeks in 50 children who were severely subnormal mentally. One group was in a special-care unit and the other group was less severely handicapped. There were 20 mongols in the study, 10 in each group. Psychological testing, including assessment of intellectual and behavioral maturity, was carried out at definite times during the study. Mental age was determined by tests and also by scores for faculties. The mean mental ages for the groups after treatment indicated that the treatment effect was not significantly greater than zero in any group of children, although it was positive in every group. Seven children (4 of whom were mongols) exhibited a large "treatment effect" on mental age, but only one case was shown to be significant. The children tested on the Griffiths Scale showed no significant responses to treatment, but showed significant natural improvements in some faculties. Of the 11 showing maximum improvement, 6 were mongols and 1 had phenylketonuria. Some of the disadvantages of treatment were increase in number of epileptic seizures; unmanageable behavior in psychotics; and restlessness, aggression, and more awareness of sex.

Hope Hospital
Salford, Lancashire, England

- 2219 Davidenkova, E. F., Kolosova, N. N., & Nekhamkina, A. G. Opyt lecheniya metildiazilom lits s zabolevaniyami nervnoy sistemy. (Experience in methylidiazyl treatment of persons with diseases of the nervous system.) *Vrachebnoe Delo*, 8:55-59, 1963.

The cholinolytic methylidiazyl was tested in 100 patients (48 males and 52 females, 18 to 47 years of age) with various diseases of the nervous system. All patients showed periods of unconsciousness, ranging from several minutes to 2 hours; headache; vertigo; and repeated vomiting. Methylidiazyl was given in doses of 1.0 cc of a 0.25% solution i.m. to 10 patients for 15 days; the remaining patients were given 0.001 g t.i.d. p.o. for 2 weeks. Within a few hours, improvement, in the form of reduction in intensity of headache and vertigo and complete relief from vomiting and motor excitation, was noted in all patients. After 2 weeks of this therapy, motor and psychic disturbances, headache, and vomiting had been completely relieved and behavior was normal. Two case histories are briefly reviewed. The drug was effective in diseases of the nervous system accompanied by increased intracranial pressure, and it had a dehydrating action. The drug effectively relieved psychic and motor excitation, insomnia, and pain in diseases of the peripheral nervous system.

Leningrad Pediatric Medical Institute
Leningrad, U.S.S.R.

- 2220 Kuhn, R. Über kindliche depressionen und ihre behandlung. (Depression in children and its treatment.) *Schweizerische Medizinische Wochenschrift*, 93:86-90, 1963.

The clinical picture of endogenous depression in children and adolescents is briefly described. Disorders of this kind are probably more frequent than is usually supposed, since they are difficult to diagnose. Their treatment, consisting of antidepressive-thymoleptic medication combined with psychotherapy, is discussed. Imipramine is the antidepressant most frequently used. Imipramine treatment is usually begun with 10 to 30 mg/day in children. Doses of 20 to 50 mg/day may be effective in adolescents, although some 12-year-olds may need higher doses (150 mg or more daily). Children are much more sensitive to imipramine than are adults, and dosage must be carefully controlled. The

severity of the condition is not a sure indication for the strength of the dose needed.

Thurgau Cantonal Therapeutic and Nursing Institution
Thurgau, Switzerland

2221 Herrera, Ernesto Garcia, Coronado, Guillermo, & Herrera, Arturo Garcia. *Valoracion del clorhidrato de cloro-3 (dimetilamino-3'propil)-10 fenotiazina en pediatria. (Evaluation of chloro-3-(dimethylamino-3-propyl)-10-phenothiazine hydrochloride in pediatrics.)* Medicina, 43:173-180, 1963.

The effects of chlorpromazine on 34 children being treated for digestive disorders (diarrhea, vomiting, colic, and hiccups) and on 26 children being treated for various respiratory disorders are reported. Sixty children with similar diagnoses served as controls and received standard therapy. All the patients improved, but the chlorpromazine patients showed more rapid improvement, lack of complications, and a notable shortening of the recuperative period. Chlorpromazine showed excellent antispasmodic, antiemetic, antipyretic, antitussive, and sedative effects. The pharmacology of chlorpromazine is briefly reviewed, including action on the CNS; potentiating actions of the drug; hypnogenic, hypothermic, antipyretic, and antiemetic actions; and absorption, fate, and excretion.

Children's Hospital
Atzacapotzalco, Mexico

2222 Hollister, L. E., Kanter, S. L., & Wright, A. *Comparison of intramuscular and oral administration of chlorpromazine and thioridazine.* Archives Internationales de Pharmacodynamie et de Therapie, 144(3-4):571-578, 1963.

Chlorpromazine and thioridazine were given in three acute doses to two groups of 12 patients each either in tablet form or prolonged action preparations of 200 mg or a single i.m. injection of 50 mg to determine which method of administration was the more potent. The clinical effects of various dose forms of the drugs were measured at determined intervals following drug administration by recording pulse rate, blood pressure, and state of consciousness. Mood changes were rated by the Clyde Mood Scale. Urinary determinations of drug accumulation were made. An i.m. dose of chlorpromazine

was about three times as potent as the same amount given p.o. Intramuscular doses of thioridazine were more comparable to the larger oral doses and were four times as potent as the orally administered drug. A smaller percentage of total drug administered was recovered in the urine over various time periods during the first 24-hour period after drug administration.

Veterans Administration Hospital
Palo Alto, California

2223 Petronio, Livio & Esposito, Sergio. *Esperienze cliniche con un nuovo derivato iminostilbenico ad azione psicotropa. (Clinical experience with a new iminostilbene derivative with psychotropic action.)* Gazzetta Internazionale di Medicina Chirurgia, 68:204-212, 1963.

The clinical effects of an iminostilbene derivative that combines the ring structure of thymoleptic imipramine and the chain structure of the neuroleptic perphenazine were tested in 70 patients with various neurovegetative and psychic manifestations (functional disturbances in cases of hyperthyroidism, pure neurovegetative dystonia, secondary dystonic states, and neurasthenic syndromes). The drug was given in doses of 150 mg/day for 3 weeks, and in some cases, for 4 to 6 weeks. Results were excellent in 34 patients, good in 28, moderate in 7, and poor in 1. The compound produced very few side effects (drowsiness in 18 cases and gastric disturbance in 2 cases). Of the neurovegetative symptoms, those of cardiovascular origin were most effectively relieved by the drug. In most of the patients, the drug modified or completely relieved the neurovegetative and psychic disturbances.

University of Pavia
Pavia, Italy

2224 Schneider, E. *Die Behandlung der dysrhythmischen Migrane und anderer Cephalaeformen mit einem neuen Kombinationsparat (Sanredo). (Treatment of dysrhythmic migraine and other forms of headache with a new combination preparation (Sanredo).)* Schweizerische Medizinische Wochenschrift, 93:1340-1343, 1963.

Ninety patients (51 females and 39 males, 13 to 70 years of age) suffering from various forms of migraine and cephalagia were treated with a drug combining dihydroergotamine methane sulfate, diphenylhydantoin, and

caffeine (Sanredo). Nearly 40% of the cases showed considerable improvement; 30% of the cases showed only minor improvement. Sanredo was most effective against classic migraine, and it exerted its effect independently of any change in EEG activity. Therapy with this combined preparation showed considerable advantage over treatment with an ergot alkaloid alone. Because of occasional side effects, the use of anticonvulsants, such as diphenylhydantoin, should be carefully controlled.

University of Basel
Basel, Switzerland

- 2225 Serra, C., Municchi, L., & Logoluso, R. Sperimentazione clinica ed elettrofisiologica di un nuovo inibitore delle monoamino ossidasi: Il CP 603. (Clinical and electrophysiological experimentation with a new monoamine oxidase inhibitor: CP 603.) *Riforma Medica*, 77:822-828, 1963.

The MAO inhibitor CP 603, the isopropylhydrazide of chlorphenoxyacetic acid, was tested in 110 psychiatric patients, who were suffering from various conditions, such as depressive states of various etiology, schizophrenia, and epilepsy. Simultaneous EEG recordings were made prior to, during, and after therapy with CP 603. Remission of the depressive state, with a slight but transitory increase in mean amplitude values and a reduction of mean frequency values in the EEG pattern, was observed in 34 patients; slight and transitory improvement of clinical symptoms was seen in 36 patients; and no improvement, or aggravation of symptoms, was seen in 40 patients. The EEG patterns for several patients in each diagnostic category are presented. The probable mechanisms of action for CP 603 are discussed in the light of recent pharmacological and clinical discoveries concerning MAO inhibitors.

Psychiatric Hospital
Bisceglie, Italy

- 2226 Gamski, Mieczyslaw. Spostrzezenia kliniczne nad zastawowaniem przetworu D₂H (Ipronal Polfa w leczeniu nerwic. (Clinical observations on the use of the D₂H preparation (Ipronal Polfa) in the treatment of neuroses.) *Polski Tygodnik Lekarski*, 18:339-343, 1963.

The effects of 5-allyl-5-hydroxypropyl barbituric acid were observed in 120 emotionally disturbed patients, 89 females

and 31 males, 18 to 74 years of age. The patients were given 0.05 to 0.10 g (as a 2% solution) of the barbiturate t.i.d. for 3 to 8 weeks, with an average of 6 weeks. Complete and long-lasting therapeutic effect was achieved in 100 patients. Three case histories are presented to illustrate the effect of the barbiturate. No side effects were noted.

Lublin, Poland

- 2227 Madalena, Jose Caruso, Ferreira, Luzitano R., & Bello, Helio. O emprego de um neuroleptico butirofenonico (haloperidol) nas psicoses agudas e cronicas. (Test of a butyrophenone neuroleptic (haloperidol) in acute and chronic psychoses.) *Revista da Associacao Medica Brasileira*, 9:(11-12):375-386, 1963.

The butyrophenone neuroleptic haloperidol was tested for clinical effect in 70 inpatients and 5 outpatients. The group of patients consisted of 43 males and 32 females, 16 to 73 years of age. Diagnoses were as follows: 46 with chronic psychosis, 29 with acute psychosis, 9 with catatonic hebephrenia, 1 with hebephrenia, and 1 with alcoholic hallucinations. Dosage was regulated according to the severity of symptoms. When the patients showed great psychomotor excitation, initial dosage was 5 to 50 mg i.v. or i.m. during the first 12 hours, with a maximum daily parenteral dose of 10 mg. In cases of less intense excitation, dosage was 5 to 10 mg p.o., with a maximum oral dose of 16 mg daily. Haloperidol exerted a rapid sedative action and produced improvement in thought processes. Because of the high potency of this drug, dosage should be carefully controlled in children and elderly patients. Correlations between antipsychotic action and production of parkinsonian effects are discussed.

Dr. Eiras Hospital
Rio de Janeiro, Brazil

- 2228 Zublin, W. Zur Behandlung schwerer kindlicher Kontaktstorungen mit Medikamenten. (Drug treatment of severe affective contact disorders in children.) *Schweizerische Medizinische Wochenschrift*, 93(2):84-86, 1963.

Large doses of chlorpromazine (150 to 300 mg/day or more) were given to six severely disturbed children, 3 to 8 years of age. The drug effects permitted contact with the

severely withdrawn children so that meaningful psychotherapy could be initiated. The children remained responsive, even when the drug was sharply reduced in dosage after administration for only 3 days.

Neuhaus Child Psychiatric Station
Ittigen bei Bern, Switzerland

- 2229 Curone, A. & Antonello, G. *Contributo nel trattamento della dismenorrea e della tensione pre-mestruale.* (Contribution to the treatment of dysmenorrhea and of premenstrual tension.) *Rivista d'Ostetricia e Ginecologia Pratica*, 45:679-689, 1963.

Because dysmenorrhea and premenstrual tension have various etiopathogenetic aspects, a study was made to find the common factors in the two forms seen clinically, the pain syndrome and premenstrual tension. Thirty cases, 21 of dysmenorrhea and 9 of premenstrual tension, were treated with the combined preparation Clitumia. The preparation contains an antispasmodic (acamylphenine dichloride), an analgesic (tolpronine dichloride), and a centrally acting sedative (scopolamine *N*-bromobutylate). The preparation was given p.o. or rectally. Results were excellent, and the drug produced no harmful side effects.

S. Giovanni Battista Public Hospital
Lonigo (Vicenza), Italy

- 2230 Cavagna, C. & Gaburri, E. *La clorobenzodiazepina (Librium) per via parenterale nel trattamento delle psicosi alcoliche acute.* (Chlorobenzodiazepine (Librium) by parenteral route in the treatment of acute alcoholic psychoses.) *Rassegna di Studi Psichiatrici*, 52:211-220, 1963.

Parenteral chlordiazepoxide was tested in the treatment of psychomotor agitation in acute alcoholic psychosis. Forty patients, 31 males and 9 females, with delirium tremens were given an initial dose of 100 mg chlordiazepoxide i.v. or i.m. Up to 600 mg of the drug was given during the first 24 hours, depending on the severity of the patient's condition. Other medications, such as vitamins, analeptics, and antibiotics, were given concomitantly. When the patient returned to consciousness and his agitation subsided sufficiently, dosage was lowered to 60 to 100 mg p.o. daily, with progressive reduction of dosage over the next 10 to 15 days. Excellent results were

achieved in 17 patients (14 males and 3 females), in 5 of whom a single injection of 100 mg chlordiazepoxide produced deep sleep for 14 to 18 hours, with substantial reduction of symptoms on awakening. The remaining patients showed progressive reduction of symptoms over a period of 3 to 5 days. Chlordiazepoxide produced no untoward side effects.

Provincial Neuropsychiatric Hospital
Varese, Italy

- 2231 Madalena, J. Caruso. *O clordiazepoxido como medicamento anti-epiléptico.* (Chlordiazepoxide as an anti-epileptic drug.) *Jornal Brasileiro de Psiquiatria*, 14:211-229, 1962.

Chlordiazepoxide was tested as an anti-epileptic drug in 25 epileptics (14 to 57 years of age) with generalized convulsive seizures, who were resistant to treatment by barbiturates, hydantoins, pyrimidines, and various combinations of these drugs. Chlordiazepoxide was given in doses of 75 to 200 mg/day p.o. Duration of treatment was 1 to 6 months, with more than half of the cases being treated for 4 months. The EEG patterns were recorded in 44% of the patients before and after chlordiazepoxide treatment. Grand-mal seizures were suppressed in 40%, reduced in 24%, unchanged in 32%, and increased in 4%. Mood and behavior improved in 72%, were unchanged in 12%, and were aggravated in 16%. Improvement in EEG activity was also noted. No toxic effects were seen, even at high doses. Side effects included drowsiness and moderate ataxia in several patients. Possible mechanisms of action for the chlordiazepoxide antiepileptic effect are described.

University of Brazil
Rio de Janeiro, Brazil

- 2232 Gnat, T., Walczak, B. Wierzbicki, T., & Zimny, S. *Wstępne wyniki leczenia chlorprotiksenem chorych psychicznie.* (Preliminary results of chlorprothixene therapy of mental patients.) *Neurologia, Neurochirurgia i Psychiatria Polska*, 13:103-106, 1963.

The effects of chlorprothixene therapy in 2 cases of involutional depression, 11 cases of schizophrenia, and 2 cases of confusional states are described. One involutional depressive was given 15 to 90 mg, chlorprothixene for 7 days, which produced

complete remission; the other was given 15 to 150 mg/day of the drug for 44 days. After 2½ months without medication, no relapses were noted. The schizophrenics were given 14 to 450 mg chlorprothixene daily for 5 to 70 days. The patients were calmed, and sleep disorders were corrected. One patient suffering from a confusional state was given 15 to 165 mg daily for 57 days; the other was given 30 to 150 mg daily for 39 days. The drug was most effective against depression and motor excitement, but it showed no effect against hallucinations and delusions. Tolerance to the drug was good.

Public Hospital for Nervous and
Psychiatric Diseases
Drewnica, Poland

- 2233 Hausner, M. & Dolezal, V. Praktické zkušenosti s halucinogeny v psychoterapii. (Practical experiences with hallucinogens in psychotherapy.) Československá Psychiatrie, 59(5):328-335, 1963.

Therapeutic mechanisms, techniques, indications, contraindications, and complications during individual and group psychotherapy when the patients are under the influence of LSD are described. The following experimental procedures were used: (1) individual LSD treatment (100µg) combined with inpatient group therapy; (2) group LSD treatment (100µg); (3) individual LSD treatment (100µg) combined with individual outpatient psychotherapy; (4) individual and group LSD therapy (100µg) combined with outpatient group psychotherapy; and (5) individual LSD treatment (50µg) combined with biographic discussions. The best results were obtained with individual LSD treatment combined with inpatient group therapy. Six paintings that were made while patients were under the influence of LSD are reproduced.

Comenius University
Prague, Czechoslovakia

- 2234 Vinař, O. Novinky v klinickém užití psychofarmak. (New experiences in the clinical use of psychotropic drugs.) Activitas Nervosa Superior, 5:93-103, 1963.

A general review is given of recent developments in the clinical use of psychotropic drugs. The effectiveness of psychotropic drugs as compared with ECT is discussed.

The Lehmani system for classification of psychotropic drugs is described. Favorable experience with centrophenoxine in the treatment of psychotic states characterized by loss of consciousness is reported. Clinical results of tests of several antidepressants (amitriptyline and imipramine) and some phenothiazines (carphenazine, butylperazine, prochlorperazine, and perphenazine) are described. Difficulties in the clinical evaluation of psychotropic drugs and the need for methods to determine the mechanisms of action of these drugs are briefly discussed. (112 references)

Psychiatric Research Institute
Prague, Czechoslovakia

- 2235 Dolecek, R. Hodnocení léčby otylosti fe a placebem v dvojitém slepém. (Evaluation of the treatment of obesity with phenmetrazine, dexphenmetrazine and placebo in a double-blind experiment.) Casopis Lekarů Ceskych, 102:934-937, 1963.

The weight-reducing properties of phenmetrazine, dexphenmetrazine, and placebo were tested in 42 obese patients. Fourteen subjects (3 men, 11 women; average age 32.3 years) were given phenmetrazine, 14 (1 man, 13 women; average age 39.7 years) were given dexphenmetrazine, and 14 (2 men, 12 women; average age 33.3 years) were given placebo. Mean original weights in all groups were 95 to 98.5 kg. All patients were placed on special diets concomitant with drug therapy. Statistical analysis showed that there was no significant difference among weight losses in the three groups during the 2-month study. After 2 months' therapy, patients on placebo and a reducing diet showed a greater weight loss (3.7 kg) than that shown during 2 months' previous treatment with a reducing diet alone (2.1 kg).

Regional Endocrinological Center
Ostrava, Czechoslovakia

- 2236 Nuyts, A. The treatment of chronic psychoses with dipiperon-R 3345. Acta Neurologica et Psychiatrica Belgica, 63:326-332, 1963.

Dipiperon (R 3345) was given in doses of 40 to 400 mg p.o. to 46 female psychotic patients, with an age range from 24 to 72 years. The patients were predominantly schizophrenics of three types---hebephrenic, paraphrenic, and catatonic. They were treated with dipiperon for 2 weeks to 5 months. In a second part of the study, the

10 patients (9 paraphrenic) who had significantly improved were studied further. Improvement occurred in the areas of autism, activity, hallucinations, and delusion. Hallucinations and delusions had disappeared in a few cases. Side effects observed were hypotension, drowsiness, fatigue, Parkinson-like syndrome, mild oculogyria, nausea, neurodyslepsy, and generalized edema. Hypotension was the most important side effect. In the second study with the significantly improved, the 10 significantly improved patients were switched to their previous medication---chlorpromazine and reserpine. The condition of six patients deteriorated after 3 weeks. Dipiperon was administered again with good results. Four paraphrenic patients were continued on their former medication. There was continued improvement in all 10 patients.

St. Antonius-Brecht
Bethaniënhuis, Belgium

2237 Leigh, W. E. J. Positive and negative placebo factors in psychopharmacodynamics. Medical Proceedings, 9(26):538-541, 1963.

In studying positive and negative placebo factors, results show that there is a very much larger placebo factor in the use of psychotropic agents than in other non-psychotropic substances. The antidrug effect concept, a sign of absence or breakdown of positive interrelationship between doctor and patient, is opposite to the new placebo effect concept and is the reversal of the placebo action concept. Symptom groups unrelated to the known actions of drug groups have been described as either positive or negative placebo effects. Therapeutic evaluation of psychotropic substances, based on animal studies, can not be equated with human response. The proper response sector of clinical trials of psychotropic substances can only be determined in human trials. The double-blind trial has many serious deficiencies and is often used to hide poorly designed and analyzed experiments.

University of Witwatersrand
Johannesburg, South Africa

2238 Matts, S. G. Flavell & Wharton, B. A.

An assessment of the value of trichlorethyl phosphate in night sedation. British Journal of Clinical Practice, 17(9):511-513, 1963.

The sedative effects of trichlorethyl phosphate (1.5 g), sodium amylobarbitol (200 mg), and an inert preparation (2 tablets) were compared in a study of 300 patients with a variety of diagnoses, but with no psychiatric diagnoses. There were 100 patients (12 to 90 years of age) in each of the three groups treated. The results showed that trichlorethyl phosphate and sodium amylobarbitol tablets produced better sedation than the placebo. The sedative effect of trichlorethyl phosphate was similar to the effect of sodium amylobarbitol. The incidence of side effects was more than three times greater in patients treated with amylobarbitol. In an extended study using 1,020 patients, trichlorethyl phosphate was given in three different preparations---tablets, effervescent tablets, and syrup. The results of the sedative effect produced by these preparations were similar. There were no adverse effects, and no cases of habituation or addiction in patients followed for 6 to 9 months occurred.

The Royal Hospital
Wolverhampton, Staffordshire, England

2239 Pare, C. M. B. & LaBrosse, Elwood H.

A further study of alleviation of the psychological effects of LSD in man by pretreatment with 5-hydroxytryptophan. Journal of Psychiatric Research, 1:271-277, 1963.

This investigation was designed to repeat previous experiments that showed that the effects of LSD, injections when preceded by 5HTP, were less than those following a similar injection preceded by saline. Thirteen healthy volunteers (18 to 25 years of age, 9 females and 4 males) were given 5HTP (25 to 60 mg i.v.) or 0.9% saline 1 hour before LSD (50µg to 60µg i.v.). The pretreatment was given in double-blind design. The Symptoms Rating Scale, given before, 1/2 hour, and 1 hour after the pretreatment, and 1/2, 1, 2, and 3-1/2 hours after LSD, showed fewer symptoms 1/2 hour after LSD administration when 5HTP was the pretreatment. The results on the Clyde Mood Scale showed an LSD effect, but no significant effect of pretreatment. These results show that 5HTP decreases the symptoms produced by LSD.

St. Bartholomew's Hospital
London, E.C.1, England

CLINICAL STUDIES 2240-2243

2240 Smulevich, A. B. & Savich, I. M.
Opyt primeneniya preparata "Ezucos" v
psikhiatricheskoi praktike. (Experiment in
the application of Esucos compound in
psychiatric practice.) Zhurnal Nevropato-
logii i Psikhiatrii, 63:767-772, 1963.

Dixyrazine (Esucos) was tested in 28 sub-
jects (12 males and 16 females, 16 to 73
years of age), 7 as inpatients and the
remaining 21 as outpatients. Diagnoses
included schizophrenia in 15 patients,
manic-depressive psychosis in 6, reactive
depression in 6, and involutional depression
in 1. Nineteen patients had received
previous treatment with psychotropic agents.
Initial dosage of dixyrazine was 10 to 31
mg, increasing to doses of 150 to 300 mg
daily in 3 to 4 days; average effective
doses ranged from 70 to 100 mg daily, and
duration of treatment was 1 to 3 months.
Ten schizophrenics responded well to
dixyrazine therapy; the five who were
resistant showed paranoid manifestation as
part of their symptomatology. All 13 depres-
sives responded well. In severe depressive
cases, dixyrazine relieved anxiety and
agitation, but did not affect mood depres-
sion. Addition of melipramine to the drug
regimen relieved this depression. The drug
was well tolerated by the majority of
patients, and no dangerous complications
were observed. Dixyrazine is recommended
for outpatient treatment.

Academy of Medical Sciences
Moscow, U.S.S.R.

2241 Tazzer, A. U. Traitement medical des
troubles convulsifs grand mal.
(Medical treatment of "grand mal" convulsive
disorders.) Scalpel, 116:867-875, 1963.

Results of a study on the effects of the
drug combination methylphenylethylhydantoin
(Mesantoin)--hydroxyzine in 100 patients, 58
males and 42 females, with cortical
dysrhythmia are reported. The patients were
given 5 to 10 cg Mesantoin t.i.d. and 10 to
50 mg hydroxyzine t.i.d. In some cases,
especially those involving substitution of
hydroxyzine for barbiturates, hydroxyzine
dosage was 300 mg daily. Duration of treat-
ment was 3 to 24 months. Two control
groups of five patients each were used. One
group was treated with 0.10 g diphenyl-
hydantoin t.i.d. combined with 20 mg hydroxy-
zine t.i.d. for 3 months; the other received
0.10 g phenylethylhydantoin t.i.d. plus 20
mg hydroxyzine t.i.d. for 3 months. Remis-
sion of grand mal seizures was obtained in
the great majority of patients and petit mal

seizures replaced grand mal seizures in 10%.
Allergic reactions occurred in three
patients.

Guadalajara, Mexico

2242 Trojanowski, Andrzej & Plewinski,
Gustaw. Przeciwwymiotne dzialanie
hydroksyzyzny u oparzonych. (Antiemetic
effect of hydroxyzine in burns.) Polski
Tygodnik Lekarski, 18:218-220, 1963.

The antiemetic effect of hydroxyzine was
tested in 13 male and 19 female burn cases.
The drug was given in a dose of 100 mg, 92
times as a prophylactic measure and 60 times
as an antiemetic. Of the 152 administrations,
the drug was ineffective only six times, and
two of these times involved the same
patient. The only side effect was dry mouth,
reported by half of the subjects.

Institute of Hematology
Lubin, Czechoslovakia

2243 Tsutsui, J. (Mechanism of cerebral
visual suppression and its treatment
by psychotropic drugs.) Journal of Clinical
Ophthalmology, 17:331-338, 1963.

Intravenous injection of amobarbital and
chlorpromazine and supplemental oral
administration of amobarbital, chlor-
promazine, meprobamate, imipramine, prometha-
zine, perphenazine, and chlorthalidone were
tested for the treatment of psychophysiologi-
cal eye disorders, such as visual neurosis,
suppression amblyopia, and vertical systag-
mus. Visual improvement was rapid in six
cases and gradual in eight. The drugs
permitted the elimination of the psycho-
physiological sight impairment so that pos-
sible difficulties in functional vision
could be tested. Possible mechanisms of
action for the visual suppression seen in
these cases are discussed. From the action
of the drugs, it is concluded that the site
of suppression is the lateral geniculate
body. Emotional suppression impulses arise
from the anterior portion of the frontal
lobe, and mechanical suppression impulses
arise from the visual association area of the
occipital lobe. These impulses are then
transferred through the thalamus and the
reticular formation to the lateral geniculate
body, where the afferent visual impulse is
depressed.

Department of Ophthalmology
Okayama Rosai Hospital
Okayama, Japan

- 2244 Prodi, M. P. & Betolotti, P.
Esperienze cliniche sull'effetto terapeutico della nialamide nel trattamento dell'enuresi infantile. (Clinical experience of the therapeutic effect of nialamide in enuresis in infants.) Rivista Sperimentale di Freniatria e Medicina Legale delle Alienazioni Mentali, 87(1): 210-215, 1963.

Nialamide was used to treat 18 hospitalized, mentally retarded (IQ 68 to 80) enuretics, 7 to 13 years of age. All 18 children were refractory to previous treatment for enuresis. Nialamide was given orally in doses of 25 to 50 mg/day. Average occurrence of enuresis per child per night before nialamide treatment was 1.424 for an 18-day period. After 22 days of nialamide treatment, occurrence of enuresis was 1.091, showing a significant difference.

(No address)

- 2245 Berrafato, V. M. **Uso della propiromazina in ostetricia.** (Use of propyromazine in obstetrics.) Revista di Ostetricia e Ginecologia, 18:317-322, 1963.

The use of propyromazine in pregnancy, labor, and puerperium is reported. The drug was given to 90 patients afflicted with severe hyperemesis, 100 patients during labor, and 60 multiparae afflicted with uterine spasms. Propyromazine given i.m. relieved vomiting in 56 of the 90 patients after the first injection. In 19 others, a second injection was necessary to relieve vomiting. Patients were given i.m. injections for 8 days, then switched to 6 tablets/day p.o. The drug was very effective during labor and in postpartum patients. There were no toxic or side effects.

Aziza Othmana Hospital
 Tunis, Tunisia

- 2246 Černý, L. **Enuresis nocturna u dětí—léčba imipraminem a její komplikace.** (The treatment of enuresis in children with imipramine and its side effects.) Activitas Nervosa Superior, 5:176-177, 1963.

Imipramine was given in the evening to 20 enuretic patients, 6 to 14 years old, in doses of 25 to 75 mg/day, depending on the weight of the patient. Very good improvement was obtained in seven cases; nine others were slightly improved; and four cases were unchanged. Significant

side effects were observed in three patients. Most important of these was a confusional state in a 12-year-old boy who had received 50 mg/day imipramine for 10 days. The patient's condition improved after suspension of the drug for 2 days. In an 11-year-old girl, imipramine therapy stopped the enuresis, but produced severe nocturnal sweating. In a 14-year-old girl, repeated vomiting followed the administration of imipramine and necessitated interruption of the course of treatment. On the basis of these results and of data contained in the literature, it is apparent that imipramine cannot replace other drugs in the treatment of enuresis; it may be used for temporary correction of disorders or as a component of complex therapy.

Children's Psychiatric Hospital
 Dolní Počernice, Czechoslovakia

- 2247 Dubois, C., Dick, P., & Rey-Bellet, J. **Un nouveau neuroleptique majeur: Le triperidol. Premiers resultats cliniques avec un nouveau derive de la serie des butyrophenones.** (A new major neuroleptic: Triperidol. First clinical results with this butyrophenone derivative.) Schweizerische Medizinische Wochenschrift, 93(45):1600-1604, 1963.

Results of clinical, biological, and EEG studies in 40 hospitalized schizophrenic patients (13 to 72 years old) treated with triperidol are reported. Triperidol was given orally (dosage not reported), and the duration of treatment was 2 to 8 months. Results are discussed according to diagnostic category. Five patients were cured; 10 were greatly improved; 19 showed slight improvement; and 6 remained unchanged. Triperidol was particularly effective against chronic hallucinatory psychoses, psychomotor inhibition, and autism. Its action was less marked in hebephrenia and paranoid schizophrenia. No age difference was seen in drug tolerance. Profuse sweating and diurnal drowsiness with nocturnal insomnia occurred in many patients during the first days of treatment. Half of the patients gained weight. The EEG and neurological effects, including chronic paroxysmic manifestations, are discussed. The drug is contraindicated in ambulatory patients because of the occurrence of excitomotor phenomena.

University of Geneva
 Geneva, Switzerland

CLINICAL STUDIES 2248

2248 De Perrot, E. Essai clinique avec l'ID 22, nouvel anti-dépressif. (A clinical trial of ID 22, a new antidepressive drug.) Psychiatria et Neurologia, 146(6):341-352, 1963.

The antidepressant ID 22 was tested in 20 inpatients (20 to 80 years of age, mean age 61 to 70 years) with depression of varied origin and hypochondria. The ID 22 combines in its molecule the side chain of the neuroleptic thioridazine and a modified imipramine ring; the pharmacology of ID 22 is briefly discussed. Optimum dosage was determined to be 60 to 80 mg daily in a single dose. Results were good in nine, fair in six, and poor in five. Concomitant medication included barbiturates for sleep given in the evening; levomepromazine was given for the treatment of anxiety in these cases. The 15 cases showing positive response received the drug for an average of 17 days (6 minimum and 21 maximum). The ID 22 exerts both a tranquilizing and, in some instances, a stimulating effect. Side effects seen in other studies in which doses of 100 to 300 mg of ID 22 were given daily are described. A reassessment of the nosology of depressive states is attempted, based on the actions of ID 22.

University of Lausanne
Lausanne, Switzerland

See also: 2137, 2139, 2141, 2143, 2144, 2145, 2151, 2152, 2154, 2156, 2157, 2158, 2159, 2161, 2162, 2250, 2256, 2281, 2364, 2401

SIDE EFFECTS

2249 Krauthammer, Von W. **Überdosierung von Medikamenten (Librium) beim Kleinkind und Möglichkeiten der EEG-Differentialdiagnostik bei angeblicher Medikamentenüberdosierung.** (Overdosage of drugs (Librium) in young children and the possibilities of EEG differential diagnosis in suspected overdosage.) Schweizerische Medizinische Wochenschrift, 93(46):1624-1626, 1963.

The EEG patterns of two suspected cases of overdosage of chlordiazepoxide in children under 2½ year of age are discussed. In the first case, a 27-month-old girl had swallowed fourteen 10-mg capsules of chlordiazepoxide. The child showed unspecific EEG changes involving homogenous and rapid dysrhythmia. The EEG tracings made a few days later were normal. In the second case, a 19-month-old girl was admitted to the hospital in a coma, suspected of having swallowed three 10-mg capsules of chlordiazepoxide. The EEG tracings revealed that the child was in an epileptic coma and was not suffering from toxic drug effects. It was confirmed that even large overdoses of chlordiazepoxide do not produce severe toxic reactions, even in infants. An EEG examination is indicated in comatose children, especially if the history of probable drug intoxication is unreliable, in order to exclude other possible causes of unconsciousness.

Basel University
Basel, Switzerland

2250 Reyss-Brion & Meyer, L. **Essai d'approche psycho-somatique de la neurotoxicité de la cyclosérine.** (An attempt at a psychosomatic approach to cycloserine neurotoxicity.) Journal de Médecine de Lyon, 44(1042):1619-1640, 1963.

The concept that the severe neurotoxic side effects of cycloserine are psychosomatic is discussed, and the application of a method of treatment of these side effects, as based on this concept, is described. Between 1956 and 1961, 105 cases of tuberculosis that were treated with cycloserine were observed for incidence and type of

side effects. Of the 105 cases, 52 showed no side effects, 24 showed minor incidents, and 29 required reduction of dosage or discontinuation of the drug. Side effects included nervous crises, character disorders, confusion syndrome, states of excitement, depressive syndrome, and schizophrenic state. Dosage of cycloserine ranged from 500 to 1,250 mg/day. Possible factors predisposing patients to psychiatric syndromes were studied. Drugs given to prevent cycloserine complications included meprobamate in 50 cases, phenobarbital in 42 cases, and neuroleptics (thioridazine, promethazine, and chlorpromazine) in 4 cases. Meprobamate was far more effective in preventing side effects than was the classic phenobarbital treatment. In a study conducted in 1961-1962, meprobamate was given with cycloserine in 56 patients. Forty-three patients showed no side effects, 5 showed minor incidents, and 8 had to discontinue cycloserine because of side effects. Cycloserine apparently has both a pharmacological and a "psychological" toxicity. Meprobamate effectively reduces the incidence of severe psychotic reactions.

(No address)

2251 Marcoulies, M., Marcelle, R., Moisse, R. Radermecker, R., Nizet, A., & Van Cauwenberge H. **Les cas d'intoxications aiguës hospitalisées à l'Institut de Médecine de l'Université de Liege (Hopital de Baviere), au cours des quatre dernières années.** (Acute hospitalizations at the University of Liege (Baviere hospital), during the past 4 years.) Acta Clinica Belgica, 18:81-115, 1963.

Six-hundred forty-seven cases of acute voluntary, accidental, and alcoholic poisoning admitted to the clinic of the University of Liege, between January 1959 and October 1962, are reviewed. A progressive use in the incidence of voluntary poisoning was seen during the 4 years; the incidence increased from 2.89% of all hospitalized cases to 5.2%. Voluntary poisoning by means of drugs was more frequent in women, and alcoholic poisoning was more frequent in

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men. Among voluntary poisoning cases, the drugs used most frequently were barbiturates, nonbarbiturate hypnotics, phenothiazines, digitalin, atropine, analgesics (salicylates, antipyrine), antiepileptics, sodium and thallium hypochlorite, and others. In accidental poisonings, drugs most frequently ingested were hypnotics, heart stimulants, analgesics, antiepileptics, atropine, sulfamides, and aspirin. The symptomatology, course, and treatment of various poisoning cases are discussed. Seventy-six cases are listed according to toxic agent, dosage, symptomatology on admission, age, sex, treatment, development of symptomatology, and outcome.

Medical Institute
Leige, France

- 2252 Huisman, J. & Vasbinder, H. Een epidemie van acute ataxie veroorzaakt door mephobarbital intoxicatie. (An epidemic of acute ataxia caused by mephobarbital poisoning.) Nederlands Tijdschrift voor Geneeskunde, 34:1721-1725, 1962.

Twenty-six cases of acute ataxia caused by accidental ingestion of mephobarbital are reported. The patients, 15 boys and 11 girls, from a few months to 7 years old, were given sulfa syrup that contained mephobarbital instead of sodium citrate. Dosage of mephobarbital was about 1,800 mg daily. The patients showed acute ataxia, torpor, hypotonia, and hyporeflexia. Duration of neurological manifestations ranged from 3 to 13 days, with an average of 6.7 days.

Gemeentelijke Geneeskundige en
Gezondheidsdienst
Rotterdam, The Netherlands

- 2253 Weber, B. & Laborit, H. Toxicite du produit G 33 040 psychotrope adrenolytique. (Toxicity of G 33,040 an adrenolytic psychotrope.) Revue Aggressologie, 3(5):731-733, 1962.

The acute and chronic toxicity of iminostilbene (G 33,040) was determined in male Wistar rats (150 to 250 g in weight). The LD₅₀ of G 33,040 was 130 mg/kg i.p. and 900 mg/kg p.o. At high doses, drowsiness appears after 15 minutes, followed by clonic convulsions at lethal doses. Symptomatology was similar for i.p. and p.o. routes of administration. Doses of 15 mg/kg/day given s.c. 6 days a week for 4 weeks produced toxic manifestations. Doses of

10 mg/kg on the same schedule produced no toxic effects. Oral administration of 111 mg/kg during a 3-month period produced no toxic effects.

93 rue de la Sante
Paris, France

- 2254 Andreoni, M. & Invernizzi, G. Su di un caso di tentato suicidio con farmaco ad azione antimonioaminossidastica. (A case of attempted suicide by the ingestion of isocarboxazid.) Giornale di Psichiatria e di Neuropatologia, 91(2):243-255, 1963.

A suicide attempt with isocarboxazid is reported in a 24-year-old man suffering from depression. The patient took 50 tablets of isocarboxazid, totaling 500 mg. One day after hospital admission, the patient was lucid, oriented in space and time, and showed only slight torpor. General and neurological examinations showed no pathology. Liver-function tests were normal. The EEG showed liability of cerebral electrogenesis, with lowered voltage of alpha rhythm. The patient reported no subjective complaints. The lack of collateral toxic effects is unusual in view of the effects of isocarboxazid reported in the literature. The patient's depression was relieved by imipramine therapy.

University of Milan
Milan, Italy

- 2255 Copinschi, C. Cornil, A., & Thys, O. Le traitement de l'intoxication barbiturique aigue. (Treatment of acute barbiturate poisoning.) Acta Clinica Belgica, 18:128-143, 1963.

After a short survey of the pharmacological properties of barbiturates and of the clinical signs of acute barbiturate poisoning, a review is given of the various methods of treatment of barbiturate poisoning presently in use. The aims of barbiturate-intoxication treatment are: (1) to diminish digestive absorption of the barbiturate; (2) to neutralize toxic action by the administration of neurostimulants; (3) to maintain vital functions within physiological limits; and (4) to speed elimination of the toxic agent. Neurostimulants discussed are: (1) the classic treatment agents—strychnine, nikethamide, picrotoxin, pentylenetetrazol, and amphetamine; (2) bemegride; (3) ethamivan; and

(4) electrical stimulation. Symptomatic treatment consists of maintaining respiratory, cardiovascular, and renal functions and of controlling body temperature. Elimination of the toxic agent is increased by induced polyurea, alkalization of plasma and urine, tromethamine, forced diuresis and alkalization of urine, and hemodialysis (the artificial kidney). The most effective method of treatment is based on the Scandinavian method of "reanimation," or maintenance of physiological functions at normal levels, and alkalization of plasma and urine by the Mollart method. Mortality is less than 3%.

St. Pierre University
Brussels, Belgium

2256 Ducrey, J. C. & Volet, B. *L'administration parenterale de Librium au cours de l'accouchement. (Parenteral administration of Librium during parturition.)* Gynaecologia, 155:221-241, 1963.

The effects of chlordiazepoxide given parenterally during labor were studied in mother and fetus in 269 deliveries. The drug was given i.m. to 102 women in doses of 25 mg and to 148 women in doses of 50 mg after dilatation reached 20 mm. The precise action of chlordiazepoxide on uterine contractions was measured in 30 patients. The curves obtained were interpreted according to the frequency of contractions and variations in amplitude and basal tonus. Lucidity and agitation in the subjects, maternal pulse, and fetal heartbeat were also observed. Chlordiazepoxide at 25 or 50 mg produced no side effect on the fetus. At 50 mg, the drug induced stupor in the mothers during labor. Preliminary trials indicate that diazepam, an analog of chlordiazepoxide, acts more effectively on uterine muscle and has none of the side effects produced by chlordiazepoxide.

University Clinic of
Gynecology and Obstetrics
Geneva, Switzerland

2257 Tudhope, G. R. *Jaundice due to drugs.* Practitioner, 191:27-33, 1963.

Drug-induced jaundice is discussed according to the type of liver damage produced by specific drugs. Three types of liver involvement are described---hepato-cellular damage, intrahepatic cholestasis, and

hemolytic jaundice. The hydrazine MAO inhibitors are most often implicated in the production of drug-induced hepatic necrosis, which can progress to fulminating, sometimes fatal, hepatitis. Liver damage from the nonhydrazine MAO inhibitors has not yet been reported. Chlorpromazine is extensively discussed as an important example of the type of drug causing jaundice characterized by intrahepatic cholestasis; other drugs producing this type of jaundice are methyltestosterone, norethandrolone, arsphenamine, phenindione, and various antibiotics. Chemical agents producing hemolysis are grouped according to the manner in which the hemolytic action occurs: (1) direct damage to circulating red cells---phenylhydrazine, phenacetin, acetanilide; (2) glutathione instability---acetylsalicylic acid, primaquine, phenacetin, phenazone; (3) immunological mechanisms---quinine, phenacetin, methoin, stibophen.

University of Sheffield
Sheffield, England

2258 *Drugs in pregnancy survey.* Practitioner, 191:775-780, 1963.

A series of 793 cases in which the result of pregnancy was miscarriage, normal fetus, abnormal fetus, stillbirth, or neonatal death are reported. These patients included 93 who had received no drugs or only iron or vitamin preparations and 700 patients who had received drugs, had had virus infections, or had had X-rays during the first 3 months of pregnancy. In the patients (661) who took one or more of the types of drugs (antihistamines, 508; phenothiazines, 164; barbiturates, 61; and females sex hormones, 60), there was a congenital abnormality rate of 3.3%, miscarriage rate of 3.6%, stillbirth rate of 1.2%, and a neonatal death rate of 0.5%. In the 93 patients who received no drugs, the congenital abnormality rate was 12%. This finding suggests that, during the term of this survey, congenital abnormalities were probably occurring in patients who had received no drugs during early pregnancy at a frequency rate equal to those patients who had received drugs.

(No address)

2259 Scott, Alfred W. *Retinal pigmentation in a patient receiving thioridazine.* Archives of Ophthalmology, 70(6):775-778, 1963.

A 19-year-old male college student, diagnosed as schizophrenic, developed retinal pigmentation while being treated with thioridazine for

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symptoms of agitation. After hospitalization, he received 50 g of thioridazine during a 3-month period, with good psychic response and no visual symptoms. Nine months later, after readmission with manic symptoms, he received in varying dosages a total of 118.5 g of thioridazine for a period of 60 days. He began to experience visual difficulties, which continued to increase in severity for a few days after medication was stopped. His continuing psychic difficulties were treated with trifluoperazine (about 30 mg/day) plus trihexyphenidyl. Six weeks post-thioridazine, his vision had improved to 20/15, and no appreciable change in the retinal pigmentation was present except for four or five areas of pigment about one-half the size of the optic disc.

Department of Ophthalmology
Massachusetts Eye and Ear Infirmary and
Harvard Medical School
Boston, Massachusetts

2260 Goldstein, Norman, Leider, Morris, & Baer, Rudolf L. Drug eruptions from anticonvulsant drugs. Archives of Dermatology, 87:612-617, 1963.

A 54-year-old white woman with a history of petit-mal seizures and a 31-year-old Negro woman with grand-mal seizure history developed cutaneous and systemic reactions due to hydantoin-type drugs and to phenobarbital. In the first case, a general physical examination, after 20 years of treatment with phenobarbital and diphenylhydantoin, led to a diagnosis of generalized osteoarthritis, generalized rheumatoid fibrositis, and synovitis of both knee joints. The skin revealed a fairly well defined, quarter sized, erythematous and edematous patch over the left eyebrow. Other erythematous areas were noted on the left ear lobe and on the left hypothenar eminence. When diphenylhydantoin was stopped, the skin changes improved greatly. The second patient developed a rash on the back and chest at the age of 22 while under treatment with diphenylhydantoin. When diphenylhydantoin was given again a year later, the woman developed a red, scaly, and tender lesion on a shoulder and on the soles. A later examination revealed that, in addition to the previously described lesion that still persisted to a large extent, she had three ulcerations on the palate and the buccal mucosa. The total impression was that this patient had a drug eruption of two types, namely, lupus-erythematosus-like and fixed, and that the cause for both lay in the anticonvulsant drugs. The patient was treated with chloroquine and with a bromide for the epileptic problems. In a few days of

chloroquine usage, the pruritus, tenderness, erythema, and scaling of the lupus-erythematosus-like lesions began to subside.

Department of Dermatology
New York University School of Medicine
New York, New York

2261 Zalis, Edwin & Pharmley, Loren F. Fatal amphetamine poisoning. Archives of Internal Medicine, 112:822-826, 1963.

A case of fatal amphetamine poisoning is described in a 22-year-old man who had ingested 140 mg of methamphetamine (28 tablets) in order to avoid military service. Ten days prior to hospitalization, the patient had been prescribed methamphetamine HCl (5 mg, 100 tablets) for depression, listlessness, and fatigue. In order to maintain blood pressure and venous fluids to correct dehydration, metaraminol and levarterenol were administered. Cortisone was given without effect. The patient presented a clinical picture of acute renal failure. Toxic effects of amphetamine included hyperpyrexia, jaundice, and vascular collapse. The effectiveness of peritoneal dialysis in removing amphetamine from the body was demonstrated. This case, as well as other fatal cases reported from amphetamine ingestion, indicates that the present estimate of the lethal dose of amphetamine drugs should be revised.

Department of Medicine
Letterman General Hospital
San Francisco, California

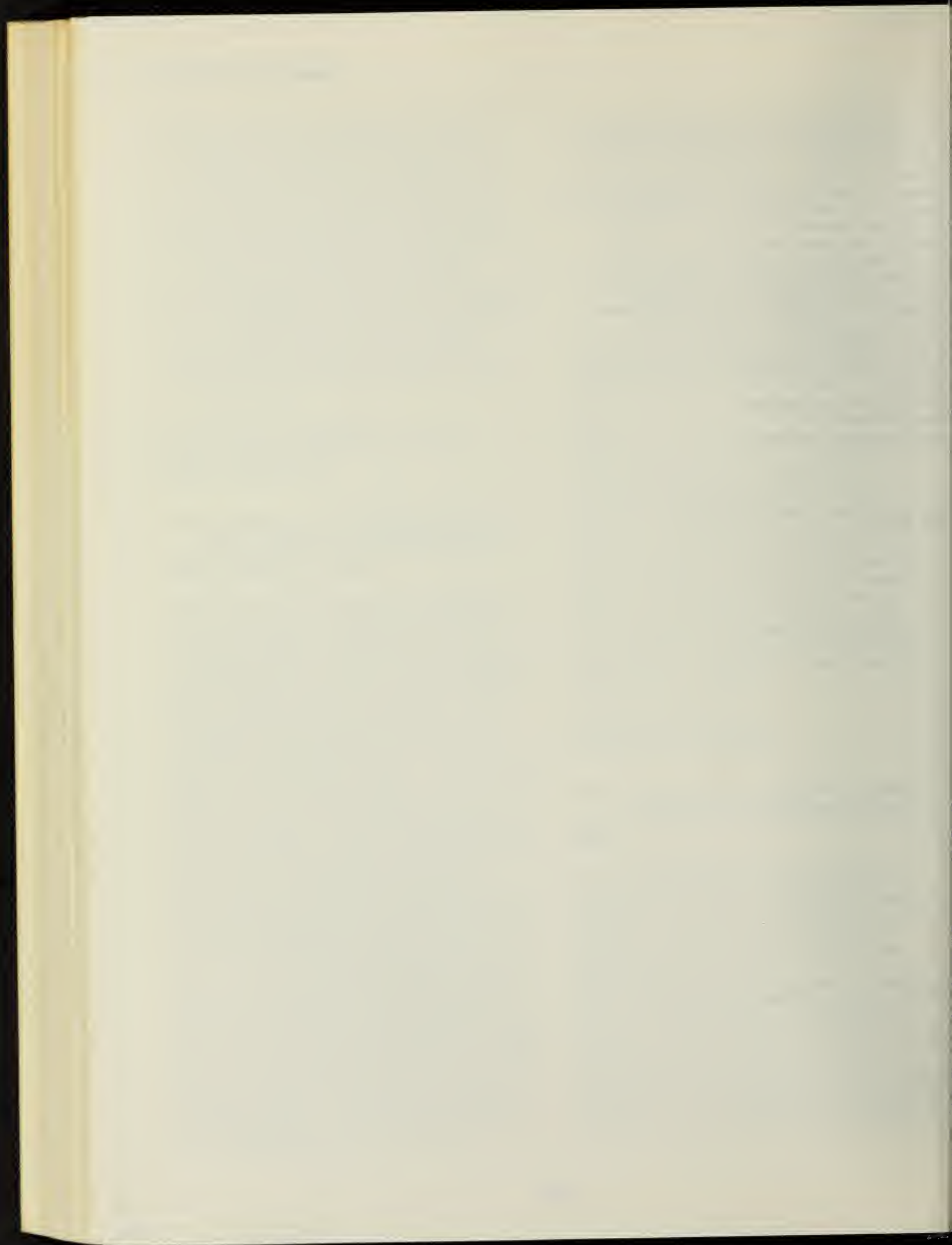
2262 Penny, John L. Megaloblastic anemia during anticonvulsant drug therapy. Archives of Internal Medicine, 111:744-749, 1963.

A case of megaloblastic anemia associated with diphenylhydantoin and phenobarbital therapy is described. A 50-year-old woman was admitted to a hospital with symptoms of increasing weakness and of shortness of breath on exertion. She had been taking diphenylhydantoin 100 mg q.i.d. and phenobarbital 60 mg q.i.d. for 17 years. Laboratory examinations, including a sternal marrow that showed megaloblastic and hyperplastic changes, revealed a packed red cell volume and hemoglobin that were below normal levels. All of the X-rays findings were normal. Diphenylhydantoin was replaced with primidone (250 mg t.i.d.), and phenobarbital therapy (60 mg q.i.d.) was continued. The patient was given a regular diet. Her diet for the

previous 2 years had been a "health diet." She was treated with cyanocobalamin 1,000 μ g i.m. every 2 days, for a total of six doses. Six weeks after her first admission, she was readmitted, and the sternal marrow was normal, as were the packed cell volume and hemoglobin. The primidone was discontinued and diphenylhydantoin (100 mg q.i.d.) and phenobarbital were reinstituted. The patient was discharged, but continued taking cyanocobalamin (100 μ g i.m. once a month). She remained well 8 months after her initial admission. The clinical syndrome, diagnosis, role of the diet and ascorbic acid in megaloblastic anemia, etiology and pathogenesis, incidence of macrocytosis, therapy, and a review of the reported cases are discussed.

44th Surgical Hospital (MA)
Korea, APO24
San Francisco, California

See also: 2144, 2145, 2155, 2202



BEHAVIORAL STUDIES

- 2263 Allen, Mary, Shannon, Gizella, & Rose, Dorian. **Thioridazine hydrochloride in the behavior disturbances of retarded children.** *American Journal of Mental Deficiency*, 68:63-68, 1963.

The purpose of this paper was to determine if thioridazine HCl decreased behavior problems in retarded children. The subjects of this double-blind experiment, 15 boys and 15 girls (8 to 16 years of age, I.Q. 3 to 78), were given either drug or placebo for 6 weeks; after this period those on the drug were given placebo and those on placebo were given the drug for an additional 6 weeks. The initial dose, 25 mg b.i.d. was increased to 25 mg t.i.d., 50 mg t.i.d., or 50 mg t.i.d. plus 100 mg at bedtime. Evaluation was made by two staff psychologists, who rated the areas of toileting, bathing, dressing, feeding, and socialization, and by the treatment personnel (ward physician, teachers, social worker), who made weekly progress notes on each patient. Patients on higher dosages of the drug did not show greater improvement than those on either 25 mg b.i.d. or 25 mg t.i.d., and when given at bedtime, the drug did not relieve either nocturnal restlessness or insomnia. Improvement noted in 16 children was related to the level of measured intelligence. Children who were mildly and moderately retarded responded better to the use of the drug.

Porterville State Hospital
Porterville, California

- 2264 Lapolla, Anthony. **Behavior reaction-time effects of benzquinamide in institutionalized psychotics.** *Clinical Medicine*, 70:1851-1857, 1963.

This study, undertaken to determine whether or not benzquinamide produced an alteration in reaction time to stimuli in psychotic patients, was conducted using 42 male psychotics (11 to 64 years of age) with neurological diseases (alcoholism, 15; psychotic reaction, 11; chronic brain syndrome, 12; personality disorders, 2; and drug addiction, 2). Benzquinamide was given at a dosage level of 50 mg q.i.d. for 5 days, after which

time the drug was increased to 100 mg q.i.d. for 3 weeks. In 11 patients, the dosage was further increased after 1 week to 200 mg q.i.d. for 2 weeks. Clinical evaluation revealed that a reduction of symptoms and improved behavior was excellent to fair in 35 patients and poor in 7 patients. The American Automobile Association Driver Training Apparatus was used to determine the effects of benzquinamide on patient alertness in a series of five tests. The average initial response time was 128 seconds before the drug, and the average final response time after 5-weeks' therapy was 87 seconds. These results indicate that benzquinamide reduced anxiety while allowing the patients to retain their total alertness and activity potential.

Santa Barbara, California

- 2265 Frankenhaeuser, Marianne, Järpe, Gundla, Svan, H., & Wrangsjö, B. **Psychophysiological reactions to two different placebo treatments.** *Scandinavian Journal of Psychology*, 4:245-250, 1963.

These experiments, aimed at examining reactions to a placebo introduced either as a stimulant drug or as a depressant drug, were designed to permit comparisons of concomitant effects on physiological functions, objective performance, and subjective reactions. Objective performance was based on the time taken to press a key in response to an auditory signal. Measurements of physiological functions, objective performance, and subjective reactions were made once before and three times after the placebo (gelatin capsule) was given to 16 healthy females (19 to 22 years of age). The depressant placebo produced a decrease in pulse rate, blood pressure, objective and subjective reaction speed, as well as feelings of depression and sleepiness. The stimulant drug produced opposite and significant changes in all variables, as well as feelings of happiness and alertness. The subjective reactions were more pronounced than the effects on performance and physiological functions.

Psychology Laboratory
University of Stockholm
Stockholm, Sweden

2266 Bleckmann, Ingrid, Jurna, Ilmar, & Rummel, Walter. Vergleichende Untersuchungen von Methoden zur Bestimmung der Plateaudauer des aktiven Zustandes am Warmblutermuskel. Verhalten des Soleus und Tibialis anterior der Katze unter Sympathicomimetica und Coffein. (Comparative studies on methods for determining the duration of the plateau of the active state in mammalian muscle. Behavior of the soleus and anterior tibial muscles in cats under the influence of sympathomimetics and caffeine.) Pfluegers Archiv für die Gesamte Physiologie des Menschen und der Tiere, 277: 422-433, 1963.

Methods for determining the duration of the plateau of the active state in mammalian muscle were compared, using cat soleus and tibialis anterior muscle and, in some cases, gastrocnemius muscle. The effect of adrenaline, noradrenaline, isoprenaline, and caffeine on this muscle behavior was recorded. Muscle tension was recorded with a strain gage or with a piezoelectric crystal. Duration of the active-state plateau was determined by tetanic stimulation or by superimposing the tension curves after a single and a double shock. The piezoelectric crystal proved to be more sensitive than the strain gage. Determination of the plateau by superimposing the two tension curves following a single and a double shock was a more reliable method than tetanic stimulation of the muscles. The duration of the plateau was 10.0 ± 0.8 msec in the soleus, 9.7 ± 0.9 msec in the tibialis anterior, and 8.5 ± 0.8 msec in the gastrocnemius muscle. Stretch of the muscles did not influence the duration of the plateau of the soleus and the tibialis anterior muscle. In the gastrocnemius muscle, however, stretch prolonged the duration of full activity. The four drugs tested had no effect on the duration of the active-state plateau. It is suggested that the effect of adrenaline on fusion frequency and tension development in the soleus and tibialis anterior muscle is not due to action on the duration of the plateau, but to an effect on the decaying phase of the active state.

Pharmacology Institute
University of the Saarland
Homburg, Germany

2267 Uliyanova, L. A. Vliyaniye tireodina i 6-metilthiouratsila na uslovnore-flektornuyu deyatel'nost' sobak s eksperimental'nym nervrozom. (Effect of thyroidin and of 6-methylthiouracil on the conditioned reflex activity of dogs with experimental neuroses.) Farmakologiya i Toksikologiya, 26:406-410, 1963.

The effects of iodothyroidin and methylthiouracil on salivation--food conditioned reflexes were studied in two dogs with experimentally induced neuroses. The neuroses were induced by overloading the processes of stimulation and inhibition. One dog showed a strongly unbalanced nervous system and the other dog showed a stable nervous system. Iodothyroidin was given in doses of 0.01 g/kg for 46 days, and methylthiouracil in doses of 0.1 g/kg for 36 days. Thyroidin experiments were performed first, followed 3 months later by the methylthiouracil experiments. In the strongly unbalanced dog, both drugs produced a marked increase in the process of stimulation. Thyroidin deepened narcosis in the stable dog. The various changes in conditioned-reflex activity in the two animals induced by the two drugs were dependent on the level of thyroid functional activity during neurosis.

Sochi Institute for the Study of Resort and Sanatorium Treatment
Sochi, U.S.S.R.

2268 Michelson, M. I. & Schelkunov, E.L. The action of chlorpromazine, chloracizine and amphetamine on the food and avoidance conditioned reflexes. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 23-30. (Psychopharmacological methods.)

The Chotin maze was used to study the motor food and avoidance conditioned reflexes in rats. Chlorpromazine was studied in 78 experiments in 11 rats with threshold disturbances of food and avoidance conditioned reflexes were noted with doses varying from 0.5 to 2.0 mg/kg. Amphetamine was used in 47 experiments using 11 rats. A complete disturbance of all conditioned reflexes, lasting for several hours, occurred after chlorpromazine in doses from 1.0 to 6.0 mg/kg. At these doses, drowsiness was evident. As a rule, doses of

0.5 to 2.0 mg/kg of amphetamine did not significantly influence the well-established conditioned reflexes. After larger doses (4.0 to 8.0 mg/kg) of amphetamine, the rats on avoidance schedule ran much faster, and the number of cases when the animal entered the maze before the conditional signal increased considerably. The food conditioned reflexes were completely abolished for a long period of time by these doses. In very large doses (8.0 mg/kg and more), amphetamine produced a peculiar disturbance of avoidance reflexes. The action of chlorpromazine in combination with amphetamine was studied in 29 experiments on 11 rats. In small doses (0.5 to 2.0 mg/kg), amphetamine can prevent or diminish the disturbance of food and avoidance conditioned reflexes produced by chlorpromazine in doses up to 2.5 mg/kg with food conditioned reflexes, and up to 6.0 mg/kg with avoidance conditioned reflexes. In larger doses (4.0 mg/kg and more), amphetamine also disturbs the conditioned reflexes. Chloracizine disturbed conditioned reflexes only in very large doses (10 to 35 mg/kg), but even with these doses, the disturbance was not as pronounced as it was with 1 to 6 mg/kg of chlorpromazine. The chloracizine-induced disturbance in conditioned reflexes was not antagonized by amphetamine.

I.M. Sechenov Institute of
Evolutionary Physiology
Academy of Sciences
Leningrad, U.S.S.R.

- 2269 Gatti, G. L. & Bovet, D. **Analysis of the action of the psychotropic drugs in a lever pressing avoidance conditioning.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 50-57. (Psychopharmacological methods.)

A study was made, using rats, of the action of psychotropic drugs in lever-pressing avoidance conditioning. The method used was based on that described by Sidman in which the animal has to make a response in order to avoid a punishment. Various drugs that are noted for their action on the reaction time of the animal, for their deconditioning activity, or for their facilitation of the learning of a conditioned behavior were

studied. The reaction time is increased by chlorpromazine, perphenazine, triflumethazine, reserpine, chlorprothixene, and by methaminodiazepoxide at times, and it is decreased by amphetamine, scopolamine, benactyzine, and imipramine. The effective response diminishes in the rats treated with chlorpromazine, perphenazine, triflumethazine, reserpine, chlorprothixene, and reserpine, and it increases with amphetamine, scopolamine, beactyzine, imipramine, and methaminodiazepoxide. The number of punishments received is increased by treatment with chlorpromazine, perphenazine, triflumethazine, chlorprothixene, reserpine, and by methaminodiazepoxide at times, and it decreases under treatment with amphetamine, scopolamine, benactyzine, and imipramine. The number of presentations of the conditioned stimulus increases when imipramine and amphetamine are given, and it diminishes under treatment with chlorpromazine, perphenazine, triflumethazine, and methaminodiazepoxide. It is not varied when scopolamine and benactyzine are given.

Instituto Superiore di Sanità
Rome, Italy

- 2270 Hecht, K. **Comparative Investigations of some centrally acting drugs with a conditioned—reflex motoric food method and a conditioned—reflex motoric escape method.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 58-69. (Psychopharmacological methods.)

A comparative investigation of the centrally acting drugs chlorpromazine (1 and 5 mg/kg), reserpine (0.1 mg/kg), and ethyl-crotylbarbiturate (5 and 35 mg/kg) was carried out, using a conditioned-reflex motor food method and a conditioned-reflex motor escape method. All drugs were administered s.c. The results are based on collective mean values of 10 animals (albino rats). Chlorpromazine (1 and 5 mg/kg) inhibited the conditioned motor escape reflex, but it did not influence the food reflexes. The differentiation of positive and negative stimulus in both methods was not significantly changed statistically. Reserpine had an inhibitory effect on the conditioned food reflexes. This applies both to the positive reactions and to the differentiation. No influence was observed on

the conditioned escape reflexes, whereas, the differentiation inhibition was intensified. Ethyl-crotylbarbiturate (5 mg/kg) inhibited the conditioned food reflexes, but it did not influence the conditioned escape reflexes. Under the action of 35 mg/kg of ethyl-crotylbarbiturate, the escape reflexes were inhibited, whereas the food reflexes had a tendency to excitation.

Institute of Cortico-Visceral
Pathology and Therapy
German Academy of Sciences
Berlin, Germany

- 2271 Jacob, J. Some effects of morphine on adaptative and learning behaviour. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November, 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 70-79. (Psychopharmacological methods.)

The actions of morphine on adaptation and/or learning under stress or conflict conditions in mice were investigated according to three methods. The methods were the hot-plate method, the forced-swimming test, and the maze performance. Licking and jumping times were measured by the hot-plate method. The substitution of an escape reaction by an avoidance response on reexposure to a thermal stimulus was depressed by morphine (0.1 to 10 mg/kg s.c.) administration, 30 minutes before the first exposure. This depressive effect differs from an analgesic action. When mice were forced to swim until exhaustion repetitively, at proper time-intervals, the performance ameliorates (adaptation). Morphine (50 mg/kg s.c.) improves first performance, but it diminishes the normally occurring amelioration at the second test. It has no action when given between the first and second launching. It appears that morphine interferes with adaptation. Mice were trained to run through a maze and leave by an abrupt descent. In the trained control mice, they climbed down without hesitation, but in the morphine-treated (5 to 50 mg/kg s.c.) animals, there is hesitation and failure to descend. These results indicate that morphine depresses the ability

of the animals to adapt themselves to a situation characterized by an unusual environment, which need not be a physically nociceptive one.

Laboratory of Pharmacology
Pasteur Institute
Paris, France

- 2272 Lapin, I. P. Comparison of imipramine and chlorpromazine effects on behavior of amphetamine-excited animals. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 80-86. (Psychopharmacological methods.)

Experiments in which adult male albino mice were used were carried out to determine the effects of imipramine and chlorpromazine on the behavior of amphetamine-excited mice. Observations were made on groups of 10 mice. Amphetamine (20 mg/kg) was administered following injections of imipramine and chlorpromazine. All drugs were administered s.c. Motor activity, aggressivity, fighting episodes, lethality within 20 hours, and death time were observed. Imipramine (10, 25, and 50 mg/kg) did not influence amphetamine toxic effects. A protective effect was exhibited with doses of 60 to 100 mg/kg. At doses of 0.5 to 1 mg/kg, the amphetamine toxicity was increased. The extremely low doses of chlorpromazine (0.001 and 0.005 mg/kg) have a "paradoxical" analeptic effect. The dependence of the effects on the dosage of chlorpromazine and imipramine is characterized by their common tendency, namely, when the dose is reduced, the replacement of the protective tranquilizing effect by the opposite analeptic effect occurs. A scheme of correlation of zones of tranquilizing and psychoanaleptic effects over a wide dose range of imipramine and chlorpromazine is discussed.

Laboratory of Psychopharmacology
Bechterev Psychoneurological Institute
Leningrad, U.S.S.R.

2273 Bättig, K. **Differential Psychopharmacological patterns of action in rats.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 151-161. (Psychopharmacological methods.)

2274 Voronin, L. G. & Napalkov, A. V. **Complex systems of conditioned reflexes in the analysis of drug effects.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 182-185. (Psychopharmacological methods.)

A method for screening behavior was set up, which consisted of a battery of learned and unlearned food- and pain-motivated responses, swimming performance, and spontaneous alternation in a simple T-maze, for the purpose of determining the mode of psychotropic action in rats of seven different drugs. The drugs used in this study include ethyl alcohol, sodium barbital, chlorpromazine, meprobamate, imipramine, caffeine sodium benzoate, and amphetamine. Two groups, each consisting of 12 male albino rats, were used. Of the five depressant drugs tested, alcohol was the only one to depress swimming performance and learned and unlearned food- and pain-motivated behavior to a similar extent. The other four depressant drugs showed the following differences as compared with alcohol: barbital improved learned and unlearned food-directed behavior; meprobamate depressed food-directed behavior to a smaller extent; and imipramine had a smaller depressant effect on learned pain-motivated responses and on unlearned food consumption. Amphetamine and caffeine had no influence on swimming performance, but they improved measures of learned and unlearned pain-motivated responses. Only amphetamine had a strong and consistent depressant effect on food-motivated behavior. Amphetamine was the only one of the seven tested drugs that disrupted spontaneous alternation, which is a normal behavioral function in rats.

The chain of motor reflexes reinforced by food and of defensive reflexes by which the dog avoids the nociceptive agent and stops its signal was used to study the effect of reserpine, caffeine, and bromide on these complex systems of conditioned reflexes. Another chain of food-seeking movements, which did not enter these systems, was formed. Reserpine (0.08 to 0.09 mg/kg) did not affect the chains of alimentary reflexes, but it inhibited the chains of defensive reflexes and depressed the efferent generalization. When caffeine (0.05 to 0.08 g/kg) was administered 30 minutes before the experiment, it did not substantially affect the chain of conditioned alimentary reflexes, whereas the effect on the chain of defensive reactions was considerable. Caffeine, in these doses, affects the course of extinction. General excitation was produced by 0.1 to 0.13 g/kg of caffeine. This dose reduced the latencies of all links of the chain of movements from 1.0 to 2.5 seconds to 0.5 to 1.0 second, and it increased the number of intersignal reactions. Repeated administration of caffeine (0.04 to 0.07 g/kg) produced inhibition in the alimentary chains of reflexes. No effects on the system of alimentary and defensive reflexes could be detected after bromide administration (0.1 to 0.5 g/kg).

Chair of the Higher Nervous Activity of the Lomonosov State University
Moscow, U.S.S.R.

2275 Froňková, K. & Chrlich, V. **The effect of psychopharmaca on higher nervous activity as revealed by autonomic reactions in dogs towards environmental stimuli.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 186-190. (Psychopharmacological methods.)

A method of chronic animal experiments was developed permitting the investigation of the mechanism of psychopharmacological

Department of Hygiene and
Physiology of Work
Swiss Federal Institute of Technology

action in peroral application in doses corresponding to body weight on the basis of current clinical usage. An assessment was made of autonomic phenomena (respiratory and pulse rates, blood pressure) at rest and of autonomic reactions in the inborn and acquired reflexes of dogs before and after drug administration. An example is given using methylphenidate in doses ranging from 0.08 to 0.93 mg/kg p.o. Three periods of drug application, each with different doses, permitted an approach to optimal doses and established qualitative differences of action depending on the amount of drug administered. It was concluded that the mechanism of the psychotonic action of methylphenidate in clinically used doses is the reinforcement of differential inhibition and also the improvement of conditioned reactions. Optimum doses of methylphenidate improved the discrimination of stimuli from the environment.

Institute for Cardiovascular Research
Prague, Czechoslovakia

- 2276 Kreindler, A. & Ungher, J. The effect of insulin on higher nervous activity. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 231-237, (Psychopharmacological methods.)

The effects of insulin (1 to 2 units/kg body weight s.c. 45 to 60 minutes before the experiment) on motor defensive and food conditioned reflexes were studied in 18 dogs. Before insulin injection, the blood sugar values ranged from 0.76 to 0.93 mg%, whereas 45 to 60 minutes after insulin administration, the minimum value was 0.30 mg%. Unconditioned defensive reflexes did not change. The positive conditioned reflexes pertaining to the defensive dynamic physiological structure (motor defensive and respiratory conditioned reflexes) and the alimentary structure (salivary conditioned reflexes) were inhibited to a varying extent. There was no disinhibition of the differentiation either in the defensive or in the alimentary physiological dynamic structure. Insulin seemed to improve differentiation in control animals possessing incomplete differentiation. In unrestrained dogs, a greater food drive was observed, indicating

an increase in unconditioned food reflex. A discussion is presented of the mechanism by which insulin affects higher nervous activity.

I. P. Pavlov Institute of Neurology of the R.P.R. Academy
Bucharest, Romania

- 2277 Ettlinger, G. High dietary tryptophan intake: Methods used to investigate possible behaviour changes in the monkey. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 238-243. (Psychopharmacological methods.)

The experimental design for studying the behavioral and neurological effects of prolonged high tryptophan intake on behavior is presented. Rhesus monkeys weighing 2 kg were used. One group of three animals received 1.5 g/day L-tryptophan for 8 weeks; another group (3 animals) received glycine; and another group (2 animals) received only the basic diet. The behavioral test program was comprised of the following three separate tests of visual shape discrimination, graded in difficulty and reflecting any changes of learning or retention: (1) a test of spatial alternation requiring short-term memory; (2) a quantitative test of the accuracy of reaching; and (3) a comprehensive neurological examination. Chemical tests involved determinations of urinary tryptophan, indole acetic acid, 5HIAA, and indoxyl sulfate by colorimetry and/or chromatography. The sequence of testing is also given.

Institute of Neurology
London, W.C.1, England

- 2278 Vinar, O. The possibilities of the use of conditioned reflex methods in clinical psychiatry. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 259-267. (Psychopharmacological methods.)

Conditioned reflex methods based on the concepts of the physiology of higher nervous activity are discussed in relation to their

use in clinical psychiatry. An attempt has been made to study reflex indicators at various functional levels, based on the Pavlovian method, on the verbal-motor method of Ivanov-Smolenskij, and on verbal-association. Interpretation of the verbal experiment is difficult in terms of the physiology of higher nervous activity. The verbal-motor method is useful but caution must be taken in interpreting the results in physiological terms. Social interaction between the experimenter and subject should be considered. In persons receiving LSD and in schizophrenics, disturbances in the cooperation of the signalling systems and phasic phenomena were observed. A prognostically important finding is the improvement in the cooperation of signalling systems during the treatment of neuroleptics. The use of skin-galvanic reflex measurements is precise, but what is actually being measured is not known. Some methods are characteristically sensitive for certain diagnostic groups, for example, the verbal motor method for schizophrenics; there are differences of sensitivity in methods for various drugs.

Psychiatric Research Institute
Prague, Czechoslovakia

2279 Cameron, D. Ewen. **The experimental method in the study of human behaviour: Central problems.** In: Society for the Study of Higher Nervous Activity. Proceedings of a symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 268-275. (Psychopharmacological methods.)

A discussion is presented of the experimental methods used in the pure sciences in relation to their application in the study of human behavior. The development of an experimental methodology adapted to human behavior and hence useful in evaluating psychotropic drugs must consider the setting in which the experiment is carried out, the experimenter, and the subject. Several attributes of the observer are presented.

Allan Memorial Institute
McGill University
Montreal, Quebec, Canada

2280 Mirsky, Allan F. & Rosvold, H. Enger. **Behavioral and physiological studies in impaired attention.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 302-315. (Psychopharmacological methods.)

In order to study the relationship between attentive behavior in man and neural mechanisms, three groups of subjects (mental defectives, and children and adults of normal intelligence, comprising in each case a brain-damaged and a non-brain-damaged subgroup) were administered the CPT (Continuous Performance Task) and a DSST (Digit-Symbol Substitution Task). In some of the tests, EEG's were carried out simultaneously with the CPT. The brain-damaged subgroups performed significantly more poorly on the CPT than did the control subgroup. With epileptic subjects, the centrencephalic group performed significantly more poorly than did those with focal epileptogenic disturbances. In an intensive study on the centrencephalic group, it was found that impaired performance tended to be associated with spike and wave episodes in the EEG. When blood-volume changes were observed, they were always in the direction of vasoconstriction. The studies of the effects of several drugs on the CPT performance revealed that meperidine, LSD-25, phenobarbital, meprobamate, and *d*-amphetamine were without significant effect on the CPT performance of normal subjects. Chlorpromazine, pentobarbital, and relatively high doses of secobarbital impaired CPT performance. Sleep deprivation studies revealed that impairment of the CPT quantitatively similar to that occurring in centrencephalic epilepsy may be produced by chlorpromazine (200 mg) or secobarbital (300 mg). The physiological variables are different for each agent. Interpretations of the relative dissociation between the behavioral and physiological effects of chlorpromazine are presented.

Division of Psychiatry
Boston University School of Medicine
Boston, Mass.

2281 Martin, Irene. The measurement of autonomic activity in depressive patients during sodium amytal sedation. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 321-325. (Psychopharmacological methods.)

This study was carried out to check the hypothesis that the establishment of the sleep threshold might prove a simple and effective means of classifying cases of depression. Measures of autonomic and muscle activity were recorded during rest and throughout the whole sedation procedure. Four groups of about 12 female subjects each (normals, endogenous depressive, reactive depressives, and an indeterminate group of depressives) were investigated. Sleep thresholds obtained by the i.v. injection of sodium amytal (0.5 mg/kg every 40 seconds) showed no significant differences between any of the groups in the amount of the drug required to reach the sleep threshold. Continuous recordings of palmar skin resistance, heart rate, and forehead muscle tension showed the forehead muscle tension levels to be higher in the patient groups than those in the normal group. Correlations between level of palmar skin resistance, heart rate, and sleep thresholds supported the assumption that subjects who are more physiologically active require larger amounts of sodium amytal to reach sleep threshold.

Institute of Psychiatry
Maudsley Hospital
London, England

2282 Cameron, D. Ewen & Solyom, L. Studies in perseveration. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 330-337. (Psychopharmacological methods.)

The phenomenon of perseveration (tendency to repeat motor activity) was studied in 31 senile and 47 arteriosclerotic individuals. To measure recent memory deficit in these patients (mean age = 71.2 years), the results obtained from the counting test were employed primarily. Perseveration presented an obstacle to the precise estimation of the span of retention in a

number of cases. Fatigue increased perseveration which appeared at the upper limits of retention. Perseveration disappeared after rest (10 minutes) and after massive reinforcement of the stimulus.

McGill University
Montreal, Canada

2283 Busfield, B. L. & Wechsler, H. Salivation as an index of higher nervous activity in diseases with prominent psychopathology. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November, 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 346-356. (Psychopharmacological methods.)

Salivation rates were determined as a possible index of higher nervous activity in 109 severely depressed hospitalized patients before they received a 4-to 8-week course of treatment with one of three antidepressant medications. The mean salivation rate of all patients was 2.01 g/2 minutes. Patients with exogenous depression (52 patients) had significantly higher rates of salivation (2.04 to 2.26 g/2 minutes) as compared with those (33 patients) with endogenous depression (1.64 to 1.91 g/2 minutes). Female depressed patients salivated at significantly lower rates than their male counterparts. Salivation rates did not vary with severity of depression in any of the diagnostic groups. One of the following antidepressants was given to each patient: isocarboxazid (20 mg/day for 2 weeks, increased to 50 mg/day), phenelzine (30 mg/day for 2 weeks, increased to 60 mg/day), imipramine (75 mg/day, increased to 185 mg/day). Also, EST was given at a rate of three treatments/week for at least 3 weeks. The 31 patients who improved on antidepressant medications had significantly higher pretreatment salivation rates as compared with 37 patients who did not improve. These results indicate that the salivation rate provides a possible means for predicting treatment success or failure on a specific biological basis.

Department of Psychiatry
Harvard Medical School
Boston, Massachusetts

2284 Steiner, W. G. & Himwich, H. E. An EEG and behavioral analysis of the anticonvulsant action of amphenidone in the rabbit. Archives Internationales de Pharmacodynamie et de Therapie, 142(1-2):1-8, 1963.

The anticonvulsant action of amphenidone, with respect to drug-induced seizures, was investigated using 91 adult New Zealand, male, albino rabbits (2 to 3 kg in weight). The EEG tracings were taken from motor and limbic cortices, caudate nucleus, thalamus, hippocampus, amygdala, and reticular substance of the brain stem in 64 animals, tracheostomized, curarized, and artificially respired before drug administration. Behavioral observations were made on 27 unoperated, freely moving animals. The following convulsant agents were given i.v. to both groups 15 minutes after premedication with i.v. amphenidone: pentylenetetrazol (15 mg/kg); picrotoxin (0.8 mg/kg); eserine salicylate (0.5 mg/kg); strychnine (0.6 mg/kg); and chlorpromazine (6 mg/kg). Seizure-threshold determinations were based on the amount of convulsant drug necessary to produce a grand mal seizure. In the curarized, artificially respired preparation, all thresholds for drug-induced seizures were elevated by amphenidone. Modifications in convulsant threshold after amphenidone (50 mg/kg) are as follows: pentylenetetrazol (40 mg/kg); picrotoxin (1.5 mg/kg); eserine salicylate (1.5 mg/kg); and strychnine (1.5 mg/kg). Amphenidone was unsuccessful in aborting a drug-induced seizure when given during the ictal stage. The development of rhinencephalic spike foci due to chlorpromazine (36 to 65 mg/kg i.v.) was not prevented by amphenidone, but it did prevent the spread of seizure activity. In the unoperated, freely moving animal, thresholds for drug-induced seizures were elevated to 15 mg/kg for pentylenetetrazol and to 1.0 mg/kg for picrotoxin by 50 mg/kg amphenidone. The tonic-clonic seizure and opisthotonus of strychnine and the muscular asthenia of eserine salicylate were not prevented by amphenidone. These results indicate that amphenidone possesses anti-convulsant activity, and its action appears to fit in with the pattern of anesthetics and hypnotics.

Thudichum Psychiatric Research Laboratory
Galesburg State Research Hospital
Galesburg, Illinois

2285 Rümke, Chr. L., Van Strik, R., De Jonge, H., & Delver, A. Experiments on the duration of hexobarbital narcosis in mice. Archives Internationales de Pharmacodynamie et de Therapie, 146(1-2):10-26, 1963.

In this report of experiments on the effect of different treatments upon the duration of a hexobarbital narcosis, randomization procedures and a chosen criterion to indicate awakening were applied. In each of two experiments on the influence of the speed of injection, 40 mice were taken from their containers in a haphazard order and were allocated to two subgroups of 20 by using a permutation of the numbers 1 to 40. Each subgroup was given 60 mg/kg hexobarbital sodium i.v. from a 3% solution in saline, in 4 or 20 seconds. Neither the duration of the narcosis nor its variability were found to be influenced by the speed of injection. In two subgroups of 15 mice, allocated by the randomization procedure, neither the duration of the narcosis nor its variability were different if 60 mg/kg hexobarbital was given i.v. from a 3% or a 2% solution. No correlation was found between the sleeping times of mice given hexobarbital (60 mg/kg i.v.) on two occasions separated by 3 days. No significant influence of weight or age on the duration of narcosis was found in animals given a hexobarbital dose on an mg/kg basis. Fifty mice were divided randomly into 5 groups of 10 and given the following treatments: Subgroup I, 70 mg/kg hexobarbital sodium s.c. on 4 successive days; Subgroup II, saline s.c. on the first day and hexobarbital s.c. on the 3 following days; Subgroup III, saline on 2 days and hexobarbital on the 2 following days; Subgroup IV, saline on 3 days and hexobarbital on the 4th day; and Subgroup V, saline on 4 successive days. It was found that the duration of narcosis decreased as the number of preceding days upon which hexobarbital had been given increased (0 to 4 days).

Department of Pharmacology
Free University of Amsterdam
Amsterdam, The Netherlands

2286 Olson, V. G. & Whittaker, J. O. Effectiveness of hydroxyzine hydrochloride in the extinction of anxiety-motivated responses. Archives Internationales de Pharmacodynamie et de Therapie, 145(1-2):288-292, 1963.

The effectiveness of hydroxyzine in extinguishing anxiety-motivated responses in rats was studied under controlled laboratory

conditions. Twenty male, albino rats (250 to 550 g) were divided into two groups and shocked repeatedly in one compartment of a dual-compartment apparatus. Following this, restraint in the shock compartment elicited a strong fear response, and cues in this compartment constituted the stimuli for escaping into the other compartment. Hydroxyzine in a dose of 70 mg/kg was then given s.c. to animals in the experimental group, and saline placebo was given s.c. to the controls. Animals receiving hydroxyzine exhibited fewer crossings from the shock to nonshock compartments during extinction than did the animals receiving placebo. Differences for succeeding 15-minute intervals were significant at less than the 0.01 confidence level.

Gustavus Adolphus College
St. Peter, Minnesota

- 2287 Plotnikoff, N. P. **Effect of psychoactive drugs on escape from audiogenic seizures.** Archives Internationales de Pharmacodynamie et de Therapie, 142 (3-4):413-420, 1963.

The effects of representatives of three classes of centrally acting drugs, phenothiazines, antidepressants, and barbiturates, were tested on the escape response of two strains of mice (DBA and Albino Swiss) susceptible to audiogenic seizures. Mice were tested during the age period of maximum seizure susceptibility (3 to 5 weeks). Two control studies were run, one in which the mice had no means of escape and one in which the mice could escape from the sound chamber. The incidence of convulsions was markedly reduced when escape was permitted. In drug studies, the drugs were given i.p. 30 to 60 minutes prior to testing. The dose that reduced the total response to 50% of the control value (PD_{50}) and its standard error were estimated by the technique of Miller and Fainter. The animals were tested in the escape situation. The phenothiazine drugs inhibited the escape response. The PD_{50} 's were 5.4 ± 0.9 mg/kg and 3.9 ± 0.6 mg/kg chlorpromazine, 2.4 ± 0.4 mg/kg and 3.5 ± 0.4 mg/kg trifluorpromazine, and 2.8 ± 0.4 mg/kg and 1.6 ± 0.2 mg/kg perphenazine for the Swiss and DBA strains respectively. The antidepressant imipramine, in doses of 10, 20, and 40 mg/kg, caused no inhibition in Swiss mice. A slight inhibition was produced in DBA mice at 40 mg/kg. Phenobarbital (2.5, 5.0, 10.0, 20.0, 40.0, and 80.0

mg/kg and pentobarbital (15.0, 30.0, and 60.0 mg/kg) caused no inhibition except at hypnotic doses.

Stanford Research Institute
Menlo Park, California

- 2288 Plotnikoff, N. P. & Fitzloff, J. **Effect of stimulants on isolated rats.** Archives Internationales de Pharmacodynamie et de Therapie, 143(3-4): 421-429, 1963.

The escape of rats from an acute auditory stress (118 db) following 28 or 56 days of isolation was tested under different conditions of drug medication. Male hooded rats of the Long-Evans strain 35 days of age were used. The test apparatus consisted of an auditory stress chamber connected to an escape chamber via a short runway. Animals isolated for 56 days showed a significant decrease in the incidence of escape compared to controls; differences in escape responses after 28 days were not significant. Rats who did not escape in the isolation studies were used in the drug experiments. Amphetamine (0.625 to 5.0 mg/kg) increased the escape response; the effect was maximal at 1.25 mg/kg. Methylphenidate (2.5 to 10 mg/kg) stimulated escape; the ED_{50} was estimated to be 5.6 ± 2.4 mg/kg. Pipradrol (2.5, 5.0, and 10.0 mg/kg) and pheniprazine (2.5, 5.0, and 10.0 mg/kg) produced no effect. Tranlycypromine (5.0, 10.0, and 20.0 mg/kg) was lethal in the two higher doses and produced no effect at 5.0 mg/kg. Caffeine (10, 20, and 40 mg/kg) also increased the escape response; the ED_{50} was estimated as 13.7 ± 3.0 mg/kg.

Stanford Research Institute
Menlo Park, California

- 2289 Plotnikoff, N. **Effect of neurotropic drugs on a non-conditioned avoidance response.** Archives Internationales de Pharmacodynamie et de Therapie, 145(3-4): 430-439, 1963.

A study is reported demonstrating that chlorpromazine can be distinguished from phenobarbital by differential inhibition of the escape response of hooded rats from intense auditory stress; the effect of other psychoactive drugs was also studied. The testing apparatus is described in detail. Chlorpromazine (1.25 to 20 mg/kg), perphenazine (1.25 to 10 mg/kg), trifluoperazine (1.25 to 5 mg/kg), prochlorperazine (1.25 to 20 mg/kg), and trifluorpromazine (1.25 to

10 mg/kg prevented escape. Phenobarbital (10 to 80 mg/kg), imipramine (10 to 40 mg/kg), promethazine (5 to 80 mg/kg), captodiamine (20 to 80 mg/kg), ectylurea (20 to 80 mg/kg), phenyltoloxamine (5 to 80 mg/kg), meprobamate (50 to 200 mg/kg), phenaglycodol (5 to 80 mg/kg), carisoprodol (50 to 200 mg/kg) did not inhibit escape. It is possible that the effects of ataractics, muscle relaxants, and sedative agents can be distinguished on the basis of the escape responses of rodents from intense sound.

Stanford Research Institute
Memlo Park, California

2290 Lang, W. J. & Gershon, S. Effects of psychoactive drugs on yohimbine induced responses in conscious dogs. A proposed screening procedure for anti-anxiety agents. Archives Internationales de Pharmacodynamie et de Therapie, 142(3-4): 457-472, 1963.

A screening technique for antianxiety agents that employs a yohimbine-induced (0.5 mg/kg i.v.) anxiety state in conscious dogs is described. In dogs, this state is similar to the responses induced by yohimbine in man. After yohimbine administration the animals became more restless, had body tremor with increased tension, and were more alert with a simultaneous increase in blood pressure and heart rate. The antianxiety agents tested were: chlorpromazine (0.5 mg/kg), chlordiazepoxide (2 mg/kg), amylobarbitol (10 mg/kg), meprobamate (10 mg/kg), and emylcamate (5 mg/kg). Other compounds used were imipramine (2.5 mg/kg), amitriptyline (1.5 mg/kg), and hexamethonium (3 to 4 mg/kg). All injections were i.v. Chlorpromazine produced a consistent fall in blood pressure, whereas there was no significant change following chlordiazepoxide, amylobarbitol, meprobamate, and emylcamate. All five antianxiety agents showed some inhibition in the rise of blood pressure, but chlorpromazine produced a significantly greater response. The following drugs were ranked in order of their antianxiety effects on behavioral changes: chlorpromazine, chlordiazepoxide, and emylcamate. Amylobarbitol and meprobamate did not produce significant effects on behavioral changes. Imipramine and amitriptyline produced sedation initially and potentiation of the yohimbine response. Hexamethonium inhibited the yohimbine rise, but the behavioral

responses were not inhibited. These results correlate with other findings of controlled clinical studies on these agents.

Department of Pharmacology
University of Melbourne
Melbourne, Australia

2291 Chittal, S. M. & Sheth, U. K.
Effect of drugs on conditioned avoidance response in rats. Archives Internationales de Pharmacodynamie et de Therapie, 144(3-4):471-480, 1963.

A comparative study is presented of the effects of tranquilizers, sedatives, analgesics, hypnotics, and stimulants on the conditioned avoidance response in 50 female, albino rats, as measured by the blocking activity on this reflex. Blocking of the unconditioned response (UR) was considered as an indication of either motor paralysis or severe toxic effect of the drug. Ten rats were used for each drug group. Morphine (1.25 to 5 mg/kg), meperidine (5 to 40 mg/kg), and codeine (4 to 32 mg/kg) showed a specific nature of action in blocking the conditioned response (CR). With cocaine (10 to 80 mg/kg), sodium salicylate (50 to 400 mg/kg), and methylphenidate (5 to 20 mg/kg), there was no blocking of the CR upon stimulation. The effects of alcohol (5% to 20%) were unique; in the lower dose range, there was no blocking action, but at 20% there was blockade of the secondary conditioned response (SR) and CR. Promethazine (1 to 100 mg/kg) caused ataxia and some blocking at the highest dosage. Chlordiazepoxide (10 to 50 mg/kg) had no effect s.c., but i.p. injections caused 10% to 20% blocking with all doses. Chlorpromazine (1 to 20 mg/kg i.p.) produced a 50% blockade of both CR and UR with 10 and 15 mg/kg, and a 100% blockade of both CR and UR with 20 mg/kg. When given orally, chlorpromazine exhibited a 50% blocking action at 20 mg. Hydroxyzine 50 to 70 mg/kg caused blocking of the CR, and with an 80 mg/kg dose, there was a blockade of both CR and UR. From these results, it is evident that this screening method has very limited parameters, which makes its usefulness doubtful for screening psychopharmacological compounds.

Seth G. S. Medical College
Bombay 12, India

- 2292 Bose, B. C., Saifi, A. Q., & Bhagwat, A. W. Effect of *Cannabis indica* on hexobarbital sleeping time and tissue respiration of rat brain. Archives Internationales de Pharmacodynamie et de Therapie, 141(3-4):520-524, 1963.

The effects of *Cannabis indica* resin on hexobarbital sleeping time and its relation to 5HT and tissue respiration in rat brain were studied, using unfasted adult rats, weighing 100 to 200 g. Hexobarbital 70 mg/kg was given to control rats. Resin (10 mg/kg) facilitates reserpine (5 mg/kg) action on hexobarbital sleeping time and antagonizes the 5HT (20 mg/kg) prolongation. *Cannabis indica* resin also depresses the tissue respirations of the rat brain. The same results were obtained from the *Cannabis indica* alcoholic extract (30 mg/kg).

Department of Pharmacology
M.G.M. Medical College
Indore, M.P., India

- 2293 Boyd, E. S., Hutchinson, E. D., Gardner, L. C., & Meritt, D. A. Effects of tetrahydrocannabinols and other drugs on operant behavior in rats. Archives Internationales de Pharmacodynamie et de Therapie, 144(3-4):533-554, 1963.

The effects of two synthetic tetrahydrocannabinols---DMHP (dimethylheptyl derivative) and MOP (methyl-octyl derivative--- and of pentobarbital (5, 10, 12.5, and 20 mg/kg), chlorpromazine (0.30, 0.62, 1.25, 2.5 mg/kg), and α -amphetamine (0.33, 0.46, 0.65, 1.25, 2.5 mg/kg) were studied on the operant behavior patterns in groups of albino rats (200 g in weight) by multiple FR(18)FI(5), multiple FR(6)FI(10), mixed FR(24)FI(5), and multiple FR(6)VI(2/3) with conditioned suppression schedules. Reserpine 0.5 mg/kg depressed behavior in the first schedule and inhibited conditioned suppression in the last schedule. Both DMHP (5 μ g to 160 μ g/kg) and MOP (20 μ g to 320 μ g/kg) depressed all measured aspects of behavior except on a mixed schedule, where they appeared to increase the ability of the animals to judge elapsed time accurately. Differentiation between various drugs by the operant technique depends on the type of schedule used and on small changes in the parameters of the schedule. In general, performance on fixed ratios was more sensitive to drugs than was performance on fixed intervals.

Department of Pharmacology
The University of Rochester
Rochester, New York

- 2294 Morris, Ralph W. Species differences in the effect of body weight on pentobarbital induced sleep. Archives Internationales de Pharmacodynamie et de Therapie, 142(3-4):550-555, 1963.

Two variables---ambient temperature and body weight---affecting barbiturate-induced sleep that is commonly used in pharmacologic screening tests, are investigated. Guinea pigs, albino rabbits, and albino mice of both sexes were injected i.p. with sodium pentobarbital (30, 30, and 60 mg/kg of body weight, respectively). The duration of sleep was determined as the time period in minutes during which the animal had lost the righting reflex. Statistically significant regression of logarithm minutes pentobarbital-induced sleep on gram body weight occurs in guinea pigs and rabbits, but not in mice. Analyses of covariance indicate that no significant effect was produced on the probability values for regression coefficients by the application to the raw data of correction factors for ambient temperature.

Department of Pharmacognosy and Pharmacology
University of Illinois
Chicago 12, Illinois

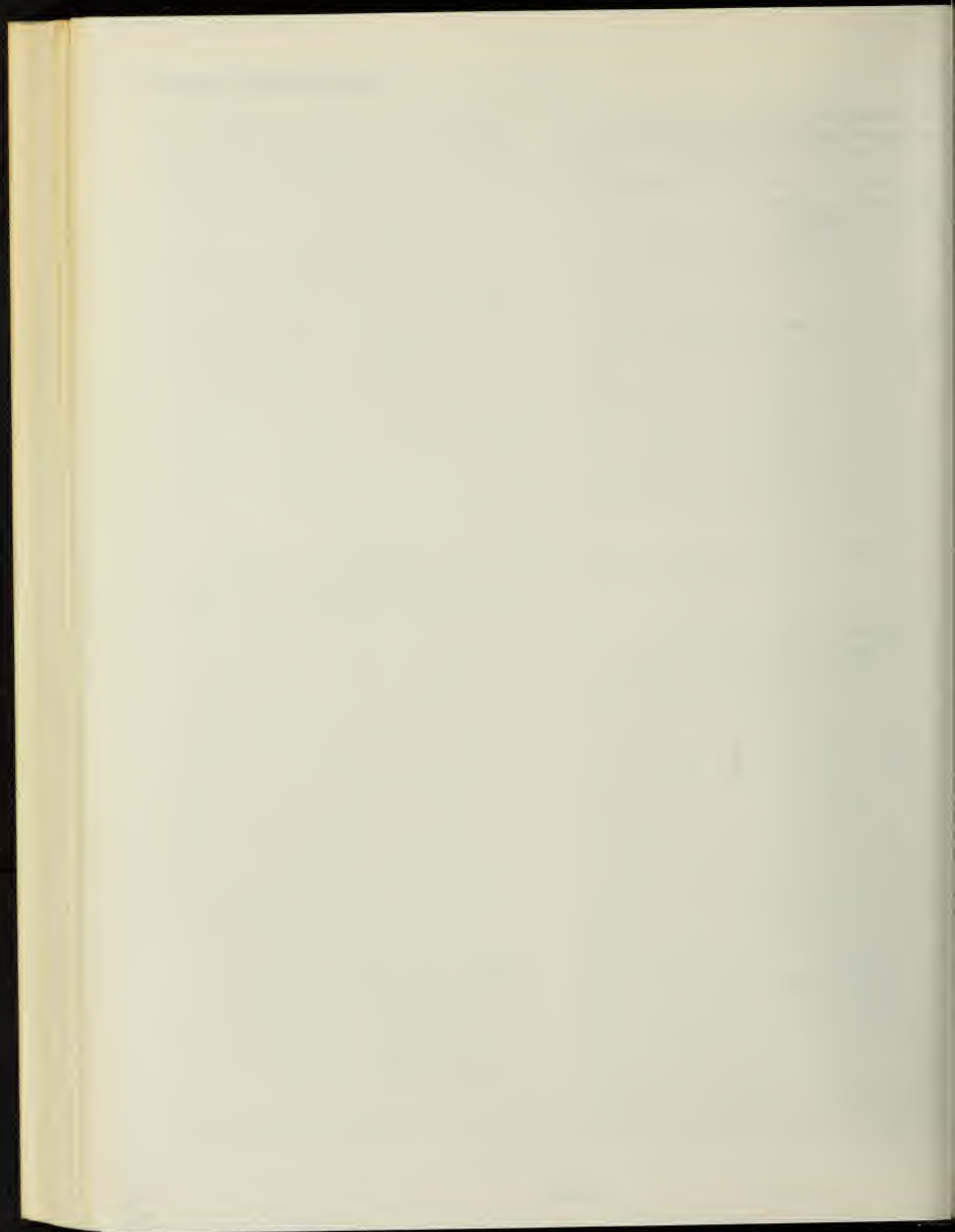
- 2295 Morris, Ralph W. Species differences in the effect of ambient temperature on barbiturate induced sleep. Archives Internationales de Pharmacodynamie et de Therapie, 141(3-4):583-590, 1963.

The relationship of ambient temperature to pentobarbital-induced sleep in mice, guinea pigs, and rabbits was investigated. Mature guinea pigs, albino rabbits, and albino mice were injected with 30, 30, and 50 mg of sodium pentobarbital i.p., respectively. Duration of sleep was determined as the time period in minutes during which the animal had lost the righting reflex. The Q_{10} method is used for making comparisons of the magnitude of the effect of temperature on chemical reactions. In this paper, Q_{10} is the factor by which a reaction velocity (units of minutes sleep per hypnotic dose of barbiturate) is increased for a 10 degree decrease in centigrade temperature. A comparison of the Q_{10} and lethality of sodium pentobarbital in mice, rabbits, rats and guinea pigs reveals that the relative lethality (LD_{50}) for i.p. sodium pentobarbital in these four species (i.e., 137, 105, 61, 55 mg/kg, respectively) parallel the relative Q_{10} values for pentobarbital-induced sleep in the same species. Mechanisms for pentobarbital hypnosis, detoxication, and death are discussed. Statistically significant regression

of log minutes pentobarbital-induced sleep on centigrade temperature occurs in mice and rabbits, but not in guinea pigs.

Department of Pharmacognosy and Pharmacology
University of Illinois
College of Pharmacy
Chicago 12, Illinois

See also: 2148, 2149, 2160, 2237, 2329,
2347



PHARMACOLOGY

- 2296 Takahashi, H. (On the action of GABA in activating physiological brain functions.) Japanese Journal of Medical Progress, 50:116-120, 1963.

The effect of GABA in activating certain complex neuron systems in the brain and the mechanism of these actions are described.

Tokyo Medical College
Tokyo, Japan

- 2297 Kao, C. Y. & Fuhrman, Frederick A. Pharmacological studies on tarichatoxin, a potent neurotoxin. Journal of Pharmacology and Experimental Therapeutics, 140(1):31-40, 1963.

The pharmacological action of purified tarichatoxin (obtained from California salamander eggs) was investigated using CF #1, C-57 B1 mice (19 to 27 g in weight), cats, New Zealand white rabbits (3 kg in weight), and the sciatic nerve and skin of frogs. The minimum lethal dose in mice was about 8 µg/kg; the LD₅₀ established graphically from the results was 10 µg/kg. Death was preceded by clonic convulsions and paralysis of skeletal and respiratory muscles. Pentobarbital (10 and 15 mg/kg) produced no significant protection against tarichatoxin. In the cat, tarichatoxin (1.4 µg/kg i.v. to 3 µg/kg i.v.) caused vaso-depression. At the low level of blood pressure, a marked pressor effect was elicited by administering either epinephrine (2 µg/kg to 6 µg/kg) or norepinephrine (8 µg/kg to 25 µg/kg). Tarichatoxin caused profound weakness of neurally elicited contractions of the nictitating membrane and skeletal muscles. It also blocked the action potential of the desheathed frog nerve. A concentration of 1 µg/l produced a partial block, whereas 10 µg/l produced a complete block. The axonal block was not preceded, accompanied, or followed by any change in the resting potential. Tarichatoxin did not exert its primary action on the effector cells or on the autonomic ganglion. The toxin (5 mg/l) produced corneal anesthesia of short duration in the rabbit's eye. The rate of oxygen consumption of the frog sciatic nerves was the same before and after

addition of the toxin (concentrations of 75 or 150 mU/ml). The toxin did not inhibit cholinesterase in concentrations of 10 to 3,000 mU/ml. It was 160,000 times more potent than cocaine in producing axonal block.

Stanford University
School of Medicine
Palo Alto, California

- 2298 Bovi, A. Prove combinati di funzionalità epatica in un gruppo di soggetti trattati con thioridazina. (Combined liver function tests in a group of patients treated with thioridazine.) Rassegna di Studi Psichiatrici, 52:312-319, 1963.

Thirteen liver-function tests were performed in 55 patients who were receiving thioridazine for the treatment of psychoneuroses of varied symptomatology, in order to determine the hepatotoxic effects of the drug. The patients, 28 males and 27 females, 16 to 55 years of age, were given 150 mg thioridazine p.o. daily, increasing to 500 mg/day maximum. The majority of cases received 300 mg/day for 20 days, with outpatient maintenance dosage of 100 mg/day for 2 to 3 months. Side effects included drowsiness, dry mouth, sweating, tachycardia, anorexia, and in a few cases, orthostatic hypotension and vertigo. Results of each of the 13 liver-function tests are discussed. These results showed that thioridazine had no toxic action on the hepatic parenchyma at therapeutic doses. The drug caused no aggravation, not even in patients with slight hepatic insufficiency.

University of Ferrara
Ferrara, Italy

2299 Votava, Z., Bennešová, O., Metyšová, J., & Soušková, M. **Drug-induced changes of higher nervous activity in experimental animals.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963, p. 31-40. (Psychopharmacological methods.)

Classical pharmacological techniques and electrophysiological and psychophysiological methods are discussed in relation to studying the effects of psychotropic drugs. The latter method is the most promising, but, at the same time, it is the most complicated part of the study of drugs. This included the use of food- and avoidance-conditioned reflexes (orientation reflexes) in animals. It is difficult, however, to transfer conclusions from animal studies to human studies because of the variation of reactivity of various species. Toxicity studies and the modification of the drug effect seem to be the most useful classical pharmacological techniques. Among the electrophysiological methods, drug-induced changes of the biopotentials in the individual regions of the intact nervous system, in certain isolated areas, in individual nervous fibers, or in the nerve cell have been studied. Only experimental tests in man can provide a correct picture of the effect of a new compound.

Research Institute for
Pharmacy and Biochemistry
Pharmacological Institute of the
Medical Faculty of Hygiene
Prague, Czechoslovakia

2300 Grushevsky, E. Ph. **Classification of medicinal and toxic substances according to the mechanism of their influence on higher nervous activity.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963. p. 41-49, (Psychopharmacological methods.)

This paper presents a classification of medicinal and toxic substances according to the mechanism of their influence on higher nervous activity. The investigated chemico-pharmaceutical substances may be divided in the following groups: (1) substances acting mostly through the excitatory process, with

clear reinforcing and weakening of the excitatory process phases, and secondary two-phased alteration of the inhibitory process; (2) substances with clear two-phased activity (reinforcing and weakening) predominantly in the inhibitory process, and secondary two-phased influence upon the excitatory process; (3) substances primarily stimulating the inhibitory process and simultaneously weakening the excitatory one, with large doses of these substances weakening both processes; and (4) substances leading, for the most part, to the weakening of inhibitory and excitatory processes without any perceptible reinforcement preceding them; these may be divided into two subgroups---substances acting directly on cortical nervous processes, and those acting indirectly on the same processes according to the type of external inhibition or disinhibition.

Department of Pharmacology
Daghestan Medical Institute
Machaczkala, U.S.S.R.

2301 Venulet, Jan. **On the correlation between the antiserotonin and the depressive action of some phenothiazine derivatives.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963. p. 87-91, (Psychopharmacological methods.)

The conditioned reflex method was used to compare the potency of chlorpromazine and acetopromazine, and to explore the effects of serotonin, iproniazid, amphetamine, picrotoxin, and caffeine on chlorpromazine and acetopromazine. Each experiment with conditioned reflex was performed on a group of 10 rats, with the conditioned stimuli (bell) being repeated 20 times with each animal. The total positive reflex reactions for the entire group of 10 animals were obtained by a single dose of the drugs. The range of doses used for chlorpromazine and acetopromazine were 2.5 to 10.0 mg/kg. Iproniazid, 5HT, amphetamine, picrotoxin, and caffeine weakened the conditioned reflex inhibition, but iproniazid and 5HT had no such influence on the action of diallylbarbituric acid. Both chlorpromazine and acetopromazine suppress the effects of 5HT on the isolated rat's uterus and stomach. The sensitivity of the stomach to phenothiazine derivatives is roughly one thousand that of the uterus. In experiments as different as those

involving conditioned reflexes and those concerned with antiserotonin action on isolated organs, the potency of acetopromazine, in either case, was roughly twice that of chlorpromazine. This may be indicative of antiserotonin action in the mechanism of conditioned reflex depression.

Drug Research Institute
Pharmacological Department
Warsaw, Poland

- 2302 Danysz, A. & Zaczek, T. X-ray radiation and psychotropic action of chlorpromazine. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 101-105. (Psychopharmacological methods.)

This study investigates the influence of irradiation on reactivity to chlorpromazine. The inhibitive action of chlorpromazine on the conditioned reflexes was examined in four groups of male, white rats, weight 120 to 180 g with 4 to 8 animals in a group and with a total of 22 animals. Chlorpromazine was injected s.c. every second day in a dose of 1.5 mg/kg and 1.25 mg/kg. After normal reactivity to chlorpromazine had been established in each group of animals, they were exposed to 300 r of X-ray radiation. A dose of 1.5 mg/kg of chlorpromazine inhibited the conditioned reflexes before irradiation by approximately 50% to 60%, and at the height of the disease, by about 80%. A dose of 1.25 mg/kg inhibited the conditioned reflexes before irradiation by approximately 29%, and after irradiation by about 86% to 98%. It was found that during the course of radiation sickness, the emotional tension of the rats did not change, but the strength of the relaxing action of chlorpromazine increased. The results show a considerable increase of chlorpromazine effects on conditioned reflexes and an increase of relaxing effects in the course of radiation sickness. It is suggested that the cause of these changes is the increased level of acetylcholine in the brain of the irradiated organism.

Department of Pharmacology
School of Medicine
Białystok, Poland

- 2303 Tonini, G., Riccioni, M. L., Babbini, M., & Missere, G. Evaluation of central pharmacological actions in rats with septal lesions. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 106-114. (Psychopharmacological methods.)

The action of central stimulants was investigated on the behavior of 400 adult, male Wistar rats; 200 of the 400 rats had lesions of septum praecommissuralis. A series of experiments was carried out on 18 animals (9 septal animals and 9 controls) to study the effect on motility of the following drugs i.p. injected: acetyl-oxy-1-phenyl-1(piperidyl-2'-)-1-methane chloride (F. I. 5949) 10 mg/kg; cocaine chloride 15 mg/kg; caffeine 20 mg/kg; methylamphetamine chloride 1 mg/kg; and methylphenidate 7.5 mg/kg. Enhancement of hypermotility after caffeine and methamphetamine was observed in the single septal rats as compared with controls. In two groups of five rats each (controls and septal animals), hypermotility, hypersexuality, and aggressiveness were observed after methamphetamine, caffeine, and methylphenidate. Three groups of 24 animals each (12 controls and 12 with septal coagulation), injected i.p. with saline, methamphetamine (0.5 mg/kg), and methylphenidate (2 mg/kg), respectively, underwent a series of 32 tests consisting of an acoustic stimulus of 30/40 volts applied to the cage grid and lasting 14 seconds. Stimulation was applied every 30 seconds and was interrupted when the animal gave the correct response. In all cases, learning was better in septal rats. It was concluded that most of the phenomena observed were due to the discontinuation in the hippocampal inhibitory circuits.

Bologna University
Bologna, Italy

- 2304 Ilyutchenok, R. J. Problems of chemical perceptibility of the brain stem reticular formation. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 115-122. (Psychopharmacological methods.)

In order to obtain the critical level of brain stem sections at which EEG activation can be observed while administering

cholinergic substances, the effects of galantamine, eserine, arecoline, and nicotine were studied in brain sections at different levels in cats. In "encephale isolé" and "cerveau isolé," administration of anti-cholinesterase and cholinomimetic substances caused EEG activation in the same manner as in the intact brain. The effect of EEG activation was observed at a higher level of the midbrain, and in the premesencephalic section, EEG was identical to "cerveau isolé." After administration of amysil (1 mg/kg), EEG activation could not be evoked, even by high doses (12 mg/kg) of galantamine, eserine, and arecoline. The data obtained showed that cholinergic systems of the reticular formation play an equal role in the activation of the cortex activity with adrenoactive systems.

Institute of Experimental Biology and Medicine of the Siberian Branch of the Academy of Sciences of the U.S.S.R.
Novosibirsk, U.S.S.R.

- 2305 Benešová, O., Bohdanecký, Z., & Votava, Z. **Electrophysiological comparison of the action of psychotropic drugs on animals with implanted electrodes.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan 1963, p. 123-128. (Psychopharmacological methods.)

The following three electrophysiological methods were used to compare the action of two thymoleptics, imipramine and its structural isomer propazepine: recording the bioelectrical activity of cortical and subcortical areas in rabbits; measuring the motor thresholds in rabbits; and measuring self-stimulation in rats. Imipramine (5 mg/kg i.v.) had a higher antagonistic effect against the physostigmine (0.1 mg/kg i.v.) EEG activity than propazepine (5 mg/kg i.v.). Imipramine (1.5 to 2 mg/kg i.v.) also produced a greater decrease of self-stimulation in rats than propazepine as (1.5 to 2 mg/kg i.v.). The potentiation of thiopental (12.5 mg/kg i.v.) narcosis as measured by motor thresholds was greater after propazepine (2.5 mg/kg i.v.) than after imipramine (2.5 mg/kg i.v.). According to the first two methods, the depressing effect of imipramine was higher, whereas according to the third method, the depressing effect of imipramine was lower than that of propazepine. It was concluded that propazepine has a

greater depressing effect on the cortical functions, and imipramine has a greater effect on the subcortical functions.

Medical College of Hygiene and Research
Institute for Pharmacy and Biochemistry
Prague, Czechoslovakia

- 2306 Horváth, M., Frantík, E., & Formánek, J. **Experimental studies of higher nervous functions in pharmacology and toxicology.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963. p. 131-150, (Psychopharmacological methods.)

A discussion of the different approaches to the study of pharmacological modification of animal behavior is presented. Animal model studies are based either upon situational analogy or upon the assumption of homologous physiological and pathological mechanisms both in animal and man. These two approaches form a basis from which the methods, the experimental design, and the method of interpretation of results are selected. How these differences work in the various components of experimental work are pointed out and discussed, especially in regard to these two types of models.

Institute of Industrial Hygiene and Occupational Diseases
Prague, Czechoslovakia

- 2307 Bohdanecký, Z., Bureš, J., Burešová, O., Nečina, J., & Weiss, T. **The use of spreading depression in neuropharmacology.** In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 191-196. (Psychopharmacological methods.)

This paper examines the possibility of using functional decortication that is achieved with spreading cortical depression—a remarkable reaction of cerebral cortex to directly acting electrical, mechanical, or chemical stimuli—for the determination of the site of drug action.

The electrophysiological signs of spreading depression indicate that cortical functions are severely impaired. Functional decortication in rats and mice can be evoked by making trephine openings over both hemispheres without piercing the dura. Filter paper soaked with potassium chloride solution is applied on the exposed cortex. Repeated waves of spreading depression prolong the duration of hexobarbital sodium or pentothal anesthesia and raise the seizure threshold of caffeine (1%), pentylenetetrazol (0.25%), and strychnine (0.002%). In unanesthetized rats, spontaneous EEG activity in tegmental reticular formation and hippocampus is not changed during cortical spreading depression, but this activity is markedly decreased under ballobarbitol (40 mg/kg i.p.) anesthesia. Spontaneous unit activity is increased in the pontobulbar reticular formation and decreased in the nonspecific thalamus. It was suggested that spreading depression may be useful in various types of neuropharmacological experiments.

Czechoslovak Academy of Sciences
Prague, Czechoslovakia

2308 Havlíček, Viktor. Some aspects of the central effect of adrenalin. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 197-208. (Psychopharmacological methods.)

The effect of adrenaline on conditioned reflexive activity (defense and feeding) and the drug's influence on the EEG and the evoked potentials were studied in rabbits and cats. Adrenaline (5 µg/kg to 50 µg/kg i.v.) produced an alteration of periods of activation with periods of deactivation in the EEG. During the activation phase following i.v. injection of 30 µg/kg of adrenaline, a marked decrease of the negative phase of evoked potential was evident. In the late deactivation period of the EEG, the amplitude of the primary evoked potential increases the negative phase. Following adrenaline (18 µg/kg), the conditioned and unconditioned feeding reflexes were completely inhibited during the phase of EEG activation, whereas the defensive reflexes were increased. Chlorpromazine (5 mg/kg) markedly blocked the activation phase of the adrenaline-effect (50 µg/kg). This supports the hypothesis that the activation phase arises from the rostral part of the reticular brain-stem formation.

Adrenaline (10 µg) applied topically to the cortex decreased the amplitude of the evoked potential. After a microinjection of 5 µg of adrenaline at a depth of 1,000 µ from the cortical surface, the positive phase of the primary response decreased significantly. Various interpretations of the mechanism of the late deactivation phase of the adrenaline effect on EEG are discussed.

Laboratory for the Research of Higher Nervous Activity
Olomouc, Czechoslovakia

2309 Floru, R., Sterescu-Volanschi, M., & Nestianu, V. Research on the psychopharmacology of norepinephrine. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 209-218. (Psychopharmacological methods.)

The effects of norepinephrine (5 µg/kg to 50 µg/kg) on the conditioned salivary reflex and conditioned motor reflex (free behavior) were investigated in 10 dogs. In a second series of experiments, using seven cats, electrodes were implanted in the mesencephalic reticular formation, posterior hypothalamus, lateral geniculate body, and motor and visual cortex in order to determine the effects of norepinephrine on the spontaneous EEG and on the biopotentials evoked by intermittent light stimulation (ILS). Doses of 20 µg/kg to 40 µg/kg norepinephrine depressed the positive conditioned reflexes. The effects of norepinephrine on the spontaneous EEG were variable. In most cases, an activation of the tracing took place. Following 2 µg/kg norepinephrine, rhythmic potentials evoked by ILS decreased in amplitude or were no longer synchronous with the rhythm of the stimulation. Higher doses of norepinephrine (20 µg/kg to 40 µg/kg) induced an evident rise in the capacity to reproduce the ILS stimulus. There was facilitation of the potentials evoked by the ILS under the action of norepinephrine (20 µg/kg to 40 µg/kg i.v.). Throughout the experiments, the animals were quiescent with no tendencies towards somnolence or restlessness.

Institute of Normal and Pathological Physiology 'D. Danielopolu' of the Academy of Rumania People's Republic
Bucharest, Rumania

2310 Hecht, K. The importance of individual excitability of the central nervous system in the investigation of centrally acting drugs. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinar, Oldřich, eds. New York, MacMillan, 1963, p. 219-230. (Psychopharmacological methods.)

The influence of individual excitability on the effect of centrally acting drugs (0.1 mg/kg/day reserpine, 5 and 35 mg/kg/day ethyl-crotyl-barbiturate) was studied, using 5- to 6-month-old albino male rats. The conditioned alimentary motor-reflex method was employed. Individual excitability was determined for each animal on the basis of values of the latencies and the inhibition-excitation ratio of various conditioned reflexes, as well as on the basis of the inhibition-excitation ratio of differential inhibition. The individual excitability ratios were determined before and after drug administration. Reserpine (0.1 mg/kg) produced a stronger inhibition in the excitable animals. Following the termination of the reserpine, a considerable after-inhibition was observed. The inhibitable animals were more strongly influenced by 5 mg/kg of ethyl-crotyl-barbiturate than were the excitable animals. A certain constancy was noted in the individual excitability of the CNS of the animals treated with 35 mg/kg of ethyl-crotyl-barbiturate. No after-inhibition was observed following termination of the drug at 5 mg/kg, but after discontinuing the drug at 35 mg/kg, the same effects were observed as those ascertained after 5 mg/kg of the drug. Interindividually significant variations were observed 2 weeks after drug discontinuation. The data indicate that the action of a centrally acting drug is not restricted to the date when it is administered, but considerable changes of the neural regulating mechanisms may be produced for subsequent weeks.

Institute of Cortico-Visceral Pathology and Therapy
German Academy of Sciences
Berlin, Germany

2311 White, R. P. Relationship between cholinergic drugs and EEG activation. Archives Internationales de Pharmacodynamie et de Therapie, 145(1-2):1-17, 1963.

An extension is made of previous studies of the central acting cholinolytic and cholinomimetic agents in antagonizing the EEG

patterns produced by EEG activating and deactivating drugs. Unanesthetized albino rabbits (1.8 to 4.2 kg in weight) were used. The EEG's were obtained, and respiratory rate and gross behavior were noted before and after drug injections. Various dose levels of pentobarbital, phenoxybenzamine, chlorpromazine, methaminodiazepoxide, morphine, atropine, and combinations of pentobarbital and phenoxybenzamine or chlorpromazine were administered to induce EEG synchrony. The EEG synchrony induced by pentobarbital in 6-mg/kg doses was employed as the standard for comparing the EEG effects obtained with other drugs. Physostigmine (0.1 mg/kg or less) not only reversed the EEG effects of 6 mg/kg of pentobarbital but also reversed the effects of all dose levels of methaminodiazepoxide, morphine, chlorpromazine, phenoxybenzamine, and combinations of the last two drugs with pentobarbital. Atropine (2 mg/kg) completely blocked the EEG effects of amphetamine, methylphenidate, LSD, caffeine, pentylene-tetrazol, and bemegride. These same stimulants reversed the EEG effects of pentobarbital. Physostigmine (0.1 mg/kg) readily antagonized all of the EEG deactivators except atropine. These results indicate the EEG alerting system contains receptors that enable cholinergic drugs to dominate the EEG effects of other agents, and that the EEG arousal mechanism is fundamentally cholinergic in nature.

Division of Pharmacology
University of Tennessee Medical Units
Memphis, Tennessee

2312 Carrier, R. N. & Buday, P. V. The influence of thyroid feeding on the pharmacologic actions of some monoamine oxidase inhibitors. Archives internationales de Pharmacodynamie et de Therapie, 145(1-2): 18-35, 1963.

Sixty male, albino Wistar rats (170 to 210 g in weight) were divided into 10 groups of 6 animals each and used to study the effect of dessicated thyroid (2%) on the pharmacodynamic actions of irreversible acting MAO inhibitors. Four groups were injected i.p. with either iproniazid (250 or 175 mg/kg/day) alone or with thyroid, and four groups were injected i.p. with pargyline alone (10 or 25 mg/kg/day) or with thyroid. Two control groups were divided into a nonmedicated group and a group that received 2% thyroid. Animals in all groups received Oleum Percomorphum, 3 drops p.o. The sluggishness and asthenia of the dually medicated animals became increasingly pronounced as the drug treatments continued (up to 3 weeks).

There was an exaggerated weight decline in the animals receiving both hormone and an MAO inhibitor. Gastrointestinal symptoms were evident in all enzyme-inhibitor-treated rats. Iproniazid (250 mg/kg) was extremely toxic, and thyroid given concurrently with the MAO inhibitor hastened death. Pargyline alone (10 and 25 mg/kg) caused no fatalities, but concurrent administration of thyroid and pargyline resulted in death of all animals within 15 days. With iproniazid (175 mg/kg) there was renal tubule necrosis, hepatocellular damage, splenic injury, and hemolysis. Only splenic darkening was observed in the pargyline-treated rats. There was a temporary rise in the blood pressure of iproniazid-treated (175 mg/kg) rats, but this occurred only after 7 days in the pargyline-dosed (10 and 25 mg/kg) animals. Thyroid alone elicited a slowly developing and uniform pressor effect. Collateral feeding of thyroid and pargyline (10 and 25 mg/kg) accelerated the onset and accentuated the pressor effects. There was no apparent correlation between the pressor responses and the excretion of dopamine. There was no significant change in the blood glucose concentrations with either one of the inhibitors and/or thyroid.

Department of Pharmacology
University of Rhode Island
Kingston, Rhode Island

- 2313 Brizzee, K. R. & Gibson, K. B.
Anti-emetic action of thiethylperazine experimental findings. Archives Internationales de Pharmacodynamie et de Therapie, 146(1-2):40-46, 1963.

The antiemetic action of thiethylperazine dimaleate (Torecan) against motion sickness in the dog and a comparison of the drug's antiemetic effect on copper sulfate emesis in the dog and cat are discussed. Fifteen dogs (9.7 to 15 kg in weight) were tested in a plywood rotation box, 30 minutes after eating. Following this, three series of 10 animals each were tested after receiving 0.15 to 0.3 mg/kg Torecan i.v. The incidence of vomiting in the controls was 87%, which was entirely inhibited by 0.03 mg of Torecan, whereas with the lower doses, the incidence was 20% in each group. The incidence of vomiting in 10 dogs given 4 mg copper sulfate p.o. was 83% in the controls, and complete protection against vomiting was produced by 0.3 and 0.2 mg/kg of Torecan i.v. Following 0.15 mg/kg Torecan, the incidence of vomiting was 30%. All 18 cats (1.42 to 4.63 kg in weight) were given a test meal of horse meat prior to the emetic. In the cat, the incidence of

vomiting at a dose of 8 mg/kg copper sulfate p.o. was reduced from 75% in the controls to 60% in animals receiving 0.03 mg/kg Torecan. A marked species difference in the effects between dog and cat is demonstrated from these results; the incidence of vomiting to a 75% effective emetic dose was reduced only 15% by 0.3 mg/kg Torecan in the cat, whereas with a 87% dose of copper sulfate in the dog, the incidence was reduced to zero with 0.3 and 0.2 mg/kg Torecan and to 30% with 0.15 mg/kg of this drug.

College of Medicine
University of Nebraska
Omaha, Nebraska

- 2314 Bhagat, B. **Effect of noradrenaline injection on the catecholamine content of the rat heart.** Archives Internationales de Pharmacodynamie et de Therapie, 146(1-2):47-55, 1963.

Studies on the uptake of noradrenaline by the heart were carried out using male albino rats of the Holtzman strain weighing 200 to 225 g. Rat-heart homogenates prepared in 0.075 M potassium phosphate buffer were separated by differential centrifugation into three fractions (coarse, particulate, and soluble) in order to ascertain whether or not the subcellular distribution of catecholamines in the rat heart is the same. About 50% of the total catecholamines present in the whole homogenate was found in the particulate fraction. When noradrenaline (1.5 mg/kg i.p.) was administered 1 hour before the animals were killed, the drug was taken up by all fractions, but the greatest uptake was in the soluble fraction. Adrenaline (0.5 to 3.0 mg/kg i.p.) produced no effect on the catecholamine levels below 1.0 mg/kg, but the uptake of noradrenaline with higher doses was proportional to the dose injected, and the concentration of cardiac catecholamines remained elevated for several hours. Bilateral adrenalectomy or suprarenal demedullation did not alter cardiac catecholamine levels or cardiac uptake of administered noradrenaline (1.5 mg/kg). This study demonstrates that the heart can accumulate large quantities of injected noradrenaline.

Department of Pharmacology and Toxicology
University of Wisconsin Medical School
Madison, Wisconsin

- 2315** Fukuyama, G. S. & Adie, P. A. **Blood levels of adrenaline and noradrenaline during anticholinesterase poisoning.** Archives Internationales de Pharmacodynamie et de Therapie, 146(1-2):56-64, 1963.

The blood concentrations of adrenaline and noradrenaline were measured in nine cats of both sexes (2.2 to 4.5 kg in weight) at various stages of sarin poisoning. Determinations were accomplished by the spectrophotofluorimetric method. The course of sarin intoxication was followed by measuring the respiration, heart rate, and blood pressure, and these three parameters were related to the concentration in the blood of the two pressor substances. Sarin (100 µg/kg s.c.) was administered. The rise in the blood concentration of adrenaline and noradrenaline occurred consistently at the time of cessation of respiration or the start of labored respiration. There was no definite relationship between blood concentrations of adrenaline and noradrenaline and blood pressure. The data appear to indicate that the primary and/or initial stimulus for the release of measurable amounts of adrenaline and noradrenaline in the blood during sarin poisoning is asphyxial in origin.

Physiology Section
Defence Research Board of Canada
Suffield Experimental Station
Ralston, Alberta, Canada

- 2316** Bhagat, B. **Effect of various monoamine oxidase inhibitors on the catecholamine content of rat heart.** Archives Internationales de Pharmacodynamie et de Therapie, 146(1-2):65-72, 1963.

The effect of MAO inhibitors on the catecholamine content in the heart was studied using male albino rats of the Holtzman strain, weighing 175 to 200 g. The rats were sacrificed following the drug injections, and the heart was homogenized. Iproniazid (100 mg/kg), pheniprazine (10 mg/kg), and MO 911 (*N*-methyl-*N*-benzylpropynylamine HCl) (100 mg/kg), i.m., all administered produced a significant increase in the catecholamine content. Reserpine (1.25 mg/kg i.m.) caused a reduction in the cardiac catecholamines, but when given after pretreatment with one of the inhibitors, the depleting action of reserpine was reduced. Chlorpromazine (5 mg/kg i.v.) given prior to noradrenaline (1.5 mg/kg i.p.) had no effect on the endogenous catecholamine levels, but it blocked the uptake of exogenous catecholamines. Chlorpromazine (20 mg/kg i.m.) given alone caused no significant change in the cardiac

catecholamines, but when given simultaneously with MAO inhibitors (iproniazid, pheniprazine, and MO 911), it reversed their elevating action of endogenous catecholamines. Possible mechanisms affecting the endogenous catecholamine accumulation in the myocardial tissue are discussed.

Department of Pharmacology and Toxicology
University of Wisconsin Medical School
Madison, Wisconsin

- 2317** O'Dell, Thomas B., Napoli, Martha D., & Mirsky, Joseph H. **Central depressant and muscle relaxant properties of a 2-substituted pyrimidine derivative.** Archives Internationales de Pharmacodynamie et de Therapie, 141(1-2):83-94, 1963.

The pharmacologic action and toxicity, both acute and subacute, of 2-β-hydroxy-β-phenethylamino-pyrimidine (I) were investigated using several species of animals, including mice, rats, dogs, and rabbits. In some instances, results obtained with the diphenyl derivative (II) are included for comparison with results with the phenyl derivative. Both I and II were found to have marked activity in the blockage of polysynaptic and monosynaptic reflexes. Other than this marked muscle-relaxant activity, the most interesting property found for these derivatives was their ability to produce a brief state of general anesthesia at relatively high dosage levels (30 to 35 mg/kg). Anesthesia is immediate upon i.v. administration and, based on loss of reflexes, appears to be greater than barbiturate anesthesia. Recovery periods were relatively short in all species tested. These compounds have no measurable analgesic or local anesthetic activity. Both normal and stimulated (α-amphetamine 4 mg/kg p.o.) motor activity of mice was depressed, with the degree of response being a function of the magnitude of the dose employed. Chlorpromazine (5 to 50 mg/kg) potentiated the anesthetic activity of these compounds. Anticonvulsant activity of phenyl derivative (I) against convulsions induced by i.v. administration of pentylene-tetrazol (35 mg/kg), strychnine (0.75 mg/kg), and nicotine (1 mg/kg) revealed a moderate but very broad range of effectiveness. No adverse effects or findings were noted at maximum daily doses of 125 mg/kg i.p. for mice and 50 mg/kg i.v. for dogs. No apparent tolerance to the depressant effects of (I) developed during 30 days.

Research Laboratories
Irwin, Neisler & Company
Decatur, Illinois

2318 Matthews, Richard J. Further studies on the neuropharmacological effects of etryptamine acetate. Archives Internationales de Pharmacodynamie et de Therapie, 142(1-2):89-110, 1963.

The neuropharmacological effects of etryptamine (*DL*- α -ethyltryptamine acetate) were studied in cats. The most obvious effect of etryptamine (10 mg/kg) on gross behavior in the cat was the intense "sympathetic-like" central excitation that occurred concomitantly with a depression of spontaneous motor activity. All central sympathetic stimulation symptoms returned to normal in 24 hours. Etryptamine depressed the ganglionic transmission (maximum depression 40% in response to 20 mg/kg), but did not block it. There was a simultaneous increase in blood pressure at 10 mg/kg. Pretreatment with 1 mg/kg of reserpine did not alter ganglionic transmission, but it did cause an increase in blood pressure. The pressor response was blocked by 1 mg/kg of hexamethonium i.v. The spinal and primary afferent pathways were not affected by etryptamine (5 to 20 mg/kg). The EEG pattern of the *cerveau isolé* was not affected by doses up to 20 mg/kg of the drug. However, in the intact cat, there was a sustained low-voltage fast activity characteristic of an arousal response at 10 mg/kg. The brain-stem lesion studies indicate that etryptamine (10 to 20 mg/kg i.v.) acts at a more caudal site in the brain-stem reticular formation, whereas amphetamine (10 mg/kg) acts on the more rostral portions of that system. No consistent effect was elicited by etryptamine (10 and 20 mg/kg) on responses evoked in the cingulate gyrus or on the surface negative dendritic potential recorded from the suprasylvian gyrus. Recruiting responses were depressed. Etryptamine was found to act primarily in the brain-stem reticular formation and the hypothalamus.

Department of Pharmacology
The Upjohn Company
Kalamazoo, Michigan

2319 Minatoya, H. Hypotensive activity of nortropine and norpseudotropine substituted phenothiazines in hypertensive and normotensive animals. Archives Internationales de Pharmacodynamie et de Therapie, 145(1-2):97-108, 1963.

The hypotensive activity and inhibitory effect of the substituted phenothiazines, 8-[3-[10-(2-chlorophenothiazinyl)]propyl]-3-hydroxynortropine (nortropine) and its

stereoisomer, pseudo-3-hydroxynortropine (norpseudotropine), on carotid occlusion and epinephrine pressor response have been compared. In 40 renal hypertensive rats (systolic blood pressure, 178 to 232 mm Hg), the hypotensive effect of the norpseudotropine (0.125 mg/kg p.o.) was significantly greater than its stereoisomer, nortropine (2 mg/kg p.o.). The duration of hypotensive action was more than 24 hours. In 30 normotensive rats (systolic blood pressure, 122 to 132 mm Hg), a slight hypotensive effect was observed with norpseudotropine (4 mg/kg p.o.), whereas nortropine (8 mg/kg p.o.) was inactive. In four trained, normotensive dogs, norpseudotropine (8 mg/kg p.o.) produced a moderate fall in diastolic and systolic blood pressure, whereas nortropine (8 mg/kg p.o.) caused a slight rise in the blood pressure of these dogs. In 32 mongrel dogs of both sexes (8 to 14 kg in weight) given alpha-chloralose (80 mg/kg, 1% solution in 0.9% saline), the adrenolytic activity of norpseudotropine ($ED_{50}=32\mu\text{g/kg}$ i.v.) was one-half that of nortropine ($ED_{50}=16\mu\text{g/kg}$ i.v.) and an injection of epinephrine ($2\mu\text{g/kg}$ i.v.). The carotid occlusion pressor response was inhibited by norpseudotropine ($45\mu\text{g/kg}$ i.v.) and by nortropine ($190\mu\text{g/kg}$ i.v.). These results indicated the greater central vasomotor component of action in norpseudotropine. The CNS depressant action was observed in norpseudotropine, but the sedative action, compared with that of its stereoisomer, was consistently less in the dog at 8 or 16 mg/kg p.o. In Swiss mice, the acute toxicities were as follows: nortropine (41 ± 2 mg/kg i.v. and 260 ± 42 mg/kg p.o.) and norpseudotropine (29 ± 1.8 mg/kg i.v. and 227 ± 37 mg/kg p.o.).

Sterling-Winthrop Research Institute
Rensselaer, New York

2320 Bose, B. C., Vijayvargiya, R., Saifi, A. Q., & Bhagwat, A. W. Chemical and pharmacological investigations of *Cannabis indica*. Part I. Archives Internationales de Pharmacodynamie et de Therapie, 146(1-2):99-105, 1963.

The chemistry and pharmacology of the resin contained in *Cannabis indica*, an intoxicant, have been investigated. The crude charas, fresh leaves, and stems were extracted with alcohol, and the resin was isolated. The resin content was found to be 29.23% in the crude charas, 7.25% in the leaves, and 3.75% in the stems. Spectrophotometric analysis revealed the maximum light absorption with pure resin, alcoholic, and carbon tetrachloride extracts at 2,800 Å, whereas in the

case of petroleum ether extract, this was observed at 2,820 Å. The pure resin (6 to 8 mg/kg) produced an inhibitory action on the respiratory movements of dogs (10 to 20 kg in weight). The resin (0.15 to 0.6 mg/ml) relaxed the plain muscles of the isolated rabbit intestine and rat uterus. The spasmogenic effects of carbachol, histamine, and pitocin (all at doses of 0.025 to 0.1 mg/ml) were antagonized by the resin, which appeared to be a direct musculotropic action.

M.G.M. Medical College
Indore, India

- 2321 Eckhardt, E. T., Plaa, G. L., & Darby, T. D. The effect of thioridazine on hepatic blood flow. Archives Internationales de Pharmacodynamie et de Therapie, 145(1-2): 109-122, 1963.

This work was designed to show that the hepatic effects seen in vitro with thioridazine can also be demonstrated in vivo, using direct portal flow measurements. The subjects, 20 healthy, mongrel dogs (15 to 22 kg in weight), were anesthetized with pentobarbital sodium (30 mg/kg i.v.), and the circulatory parameters (blood flow, blood pressure, and myocardial isometric systolic tension) were measured. Thioridazine (4 mg/kg i.v.) caused a prolonged decrease in portal flow and a concomitant increase in portal pressure. This response was more pronounced when given intraportally than when given into a peripheral vein. A decrease was observed in thoracic vena caval flow, cardiac output, aortic pressure, right arterial pressure, right arterial pressure, and abdominal caval pressure. Spinal cord blockade and reserpinization (0.1 mg/kg b.i.d. for 5 days i.m.) did not alter the overall response to thioridazine. Tolerance developed to the portal flow response, but not to the portal pressure response. The effects of epinephrine HCl (1 µg/kg), norepinephrine HCl (1 µg/kg), isoproterenol HCl (0.5 µg/kg), methoxamine HCl (100 µg/kg), and nitroglycerine (30 µg/kg) were also investigated for comparative purposes. Isoproterenol and epinephrine caused an elevation in portal flow and pressure; the former drug increased right arterial pressure, whereas the latter drug decreased arterial pressure. Methoxamine decreased portal flow, increased portal pressure, and decreased right arterial pressure. Nitroglycerine decreased portal flow, increased right arterial pressure, and showed a biphasic response to portal pressure.

Tulane University
New Orleans, Louisiana

- 2322 Efron, D. H. & Gessa, G. L. Failure of ethanol and barbiturates to alter brain monoamine content. Archives Internationales de Pharmacodynamie et de Therapie, 142(1-2):111-116, 1963.

Investigations on the effects of ethanol and barbiturates on rabbit and rat brain amine levels have been reported. White adult, male rabbits (2 to 3 kg in weight) and adult, male Sprague-Dawley rats (180 to 22 g in weight) were given ethanol (2 g/kg i.v. as a single dose or daily for 7 days), phenobarbital (100 mg/kg i.p.), or pentobarbital (50 mg/kg i.p.). The ethanol given in a single dose or chronically did not alter the serotonin and norepinephrine levels in the rabbit or the rat brain. Phenobarbital and pentobarbital did not change the serotonin levels in the rat brain.

National Heart Institute
National Institutes of Health
Bethesda, Maryland

- 2323 Bose, B. C., Vijayvargiya, R., Saifi, A. Q., & Sharma, S. K. Effect of reserpine on amino acids in brain. Archives Internationales de Pharmacodynamie et de Therapie, 146(1-2):114-118, 1963.

The effects of reserpine on the individual and total amino acids and on amino nitrogen content of the rat brain were studied. Eighty albino rats of either sex, weighing 100 to 150 g, were used in the experiments, and 20 of these rats were used as controls. Reserpine (1 to 5 mg/kg i.p.) reduced both amino nitrogen and total amino acid by 15%. A decrease in glutamic acid and tyrosine concentrations was observed after reserpine (5 mg/kg) administration by 43% and 45%, respectively. Both γ-aminobutyric acid and aspartic acid levels increased by 21% and 23%, respectively, at the same dose level. Histidine, tryptophan, and 5HTP concentrations were diminished to a moderate degree, whereas D,L-phenylalanine, proline, and hydroxyproline levels were not significantly affected. Oxidation, transamination, and decarboxylation may be the processes involved in reserpine action.

M.G.M. Medical College
Indore, India

2324 Weaver, Lawrence C., Jones, W. Ralph, & Kerley, T. Lamar. Some central nervous system depressant properties of 2-methyl-3-o-tolyl-4(3H)-quinazolinone (TR-495). *Archives Internationales de Pharmacodynamie et de Therapie*, 143(1-2):119-126, 1963.

The CNS depressant properties of 2-methyl-3-o-tolyl-4(3H)-quinazolinone (TR-495) were tested in male albino, Swiss-Webster mice (18 to 25 g in weight). Adult mongrel dogs and male albino Wistar rats were used in some experiments. The TR-495 (10 to 100 mg/kg i.g.) enhanced the depressant effects of hexobarbital (100 mg/kg i.p.) and ethanol (4 g/kg i.p.). The TR-495 (200 mg/kg i.g.) produced sleep in mice comparable to glutethimide (400 mg/kg i.g.) and chlor-diazepoxide (500 mg/kg i.g.). Glutethimide (200 mg/kg i.g.) and chlordiazepoxide (200 mg/kg i.g.) enhanced the depressant effect of TR-495 (100 mg/kg i.p.), whereas amphetamine (10 mg/kg i.p.) antagonized the effect. Anti-pentylentetrazol effects were shown by TR-495 (28 mg/kg p.o.), but no appreciable effect against strychnine (2.0 mg/kg i.p.) was observed. Antagonism of tremors induced by tremorine was observed after TR-495 (40 and 8 mg/kg i.g.). At 100 mg/kg of TR-495, a profound lowering of body temperature was observed. There were no apparent differences noted between 100 and 400 mg/kg. It was concluded that TR-495 is a moderately potent CNS depressant.

Pitman-Moore Company
Indianapolis, Indiana

2325 Madan, B. R., Sharma, J. D., & Vyas, D. S. Actions of methaminodiazepoxide on cardiac, smooth and skeletal muscles. *Archives Internationales de Pharmacodynamie et de Therapie*, 143(1-2):127-137, 1963.

Methaminodiazepoxide has been investigated for its actions on cardiac, smooth, and skeletal muscles. In the rabbit's intestine, the dog's trachea, the rat's uterus, and the frog's rectus, methaminodiazepoxide (100 µg/ml) caused a marked decrease in the response to acetylcholine (0.5 µg/ml). Sinus rate and contractility of the rabbit's auricles and frog's heart were reduced by methaminodiazepoxide in concentrations as high as 10 mg%, but there was no antagonism to the inhibitory effect of acetylcholine on the auricles. In the intact, anesthetized mongrel dog (10 to 14 kg), methaminodiazepoxide (5 to 15 mg/kg i.v.) caused transient depression of blood pressure, heart rate, and myocardial contractility without any

appreciable change in the P-Q and Q-T intervals of the ECG. There was no beneficial effect in auricular fibrillation or flutter induced by acetylcholine (5%) and injury stimulation, respectively, in dogs (10 to 18 kg) when methaminodiazepoxide (10 mg/kg i.v.) was administered. Methaminodiazepoxide (10 to 30 mg/kg i.v.) was effective in suppressing ventricular ectopic tachycardia following two-stage coronary ligation in dogs. The results and low toxicity of methaminodiazepoxide suggest the possible usefulness of the drug in selected cases of ventricular arrhythmias.

Medical College
Bikaner, India

2326 Urquiaga, X., Villarreal, J., Alonso-DeFlorida, F., & Pardo, E. G. On the ganglionic actions of certain anti-depressant drugs. *Archives Internationales de Pharmacodynamie et de Therapie*, 146(1-2):126-133, 1963.

A study was made on the effects of several antidepressant drugs on the postganglionic spike potentials evoked by single supra-maximal stimuli applied to the preganglionic fibers of the superior cervical ganglion of cats (1.0 to 3.5 kg). All drugs were administered in saline as continuous i.v. infusions for 30-minute periods. Iproniazid produced ganglionic blockade at infusion rates of 200 mg/kg/minute (20%), 400 mg/kg/minute (50%), and 4.0 mg/kg/minute (25%). Nialamide (4.0 mg/kg/minute) showed an activity of the same order as that of iproniazid. Phenelzine produced a slight blockade of transmission at 0.8 mg/kg/minute; at 0.4 mg/kg/minute, it produced a blockade greater than that obtained with the highest dose of iproniazid. A slight decrease in spike potentials was produced by phenylisopropylhydrazine (0.08 mg/kg/minute), but it produced less blockade at 0.8 mg/kg/minute than that of phenelzine (0.4 mg/kg/minute). Imipramine produced clear blockade at 0.08 mg/kg/minute and was as active as phenylisopropylhydrazine at 0.8 mg/kg/minute. With iproniazid, phenelzine, and imipramine, blockade occurred quickly and seemed to have reached a maximum at the end of the 30-minute period. Pretreatment of cats with iproniazid (20 mg/kg p.o.) either 2 hours or 24 hours before continuous infusion of epinephrine (0.2 µg/kg/minute or 2.0 µg/kg/minute) for 30 minutes did not increase the blockade action of epinephrine. Ganglionic blockade was demonstrated with all compounds tested, but the results indicate that this

action is not related to MAO inhibition by these drugs and is probably of no significance in the clinical use of these compounds.

University of Michigan
Ann Arbor, Michigan

- 2327 Ross, Charles A., Wenger, Herbert C., Ludden, Carl T., & Stone, Clement A. Selective potentiation of sympathomimetic amines by reserpine, syrosingopine and 2,6-xylylcholine ether bromide (TM-10) in the dog. *Archives Internationales de Pharmacodynamie et de Therapie*, 142(1-2):141-151, 1963.

Several drugs were investigated for their selective potentiation of sympathomimetic amines in anesthetized, vagotomized dogs. Reserpine (0.20 mg/kg i.v.), syrosingopine (0.20 mg/kg i.v.), and 2,6-xylylcholine ether bromide or TM-10 (5.0 mg/kg i.v.) caused marked potentiation of vasopressor responses to phenethylamine (50 µg/kg i.v.) and tyramine (100 µg/kg i.v.). Norepinephrine (1 µg/kg i.v.) and dopamine (50 µg/kg i.v.) pressor responses were not enhanced to any appreciable extent. The enhanced pressor responses of phenethylamine were demonstrated 10 minutes after the drug's administration and were maintained for 80 to 100 minutes. That the effects on phenethylamine were dosage related was demonstrated by experiments in which the pressor response was measured before and after 0.1 and 0.5 mg/kg of reserpine and syrosingopine. Reserpine and syrosingopine were equipotent, and both were 40 times more potent than TM-10. None of the other drugs tested, in the doses used, approached the effectiveness of syrosingopine, reserpine, and TM-10. These drugs are as follows: bretylium (1.25 to 5.0 mg/kg i.v.), guanethidine (1.25 to 10.0 mg/kg i.v.), methyldopa (25.0 to 100.0 mg/kg i.v.), α-methyl-*m*-tyrosine (25.0 to 100.0 mg/kg i.v.), iproniazid (50.0 mg/kg i.v.), phenylisopropyl hydrazine (5.0 mg/kg i.v.), cocaine (0.125 to 4.0 mg/kg i.v.), and pyrogallol (20.0 to 40.0 mg/kg i.v.). It was suggested that the phenomenon described was due to a sensitizing action on the catecholamine stores upon which phenethylamine is presumed to act.

Merck Institute for Therapeutic Research
West Point, Pennsylvania

- 2328 Borzelleca, J. F. The influence of saline and glucose infusions on the course of acute barbiturate intoxication. *Archives Internationales de Pharmacodynamie et de Therapie*, 146(1-2):163-173, 1963.

These studies were undertaken to determine the effectiveness of diuresis, induced by various procedures or agents, on the course of acute intoxication of a short-acting barbiturate, pentobarbital, and of a long-acting barbiturate, barbital. Artificial respiration (stroke volume: 25 cc/kg; rate: 20/minute) exerted a protective effect in adult, male and female mongrel dogs infused with pentobarbital sodium (1 mg/kg/ml) or barbital sodium (5 mg/kg/ml). Infusions of saline (0.9% weight/volume) or glucose (5.5% weight/volume) administered in conjunction with artificial respiration increased the protective effects of the latter. The saline and glucose apparently protected the cardiovascular system from the depressant effects of the barbiturates. The mechanisms of the protective effects of the infusions do not involve primarily an increase in circulating fluid nor a diuretic effect; an effect on the distribution, metabolism, and/or excretion of the barbiturates may be involved.

Medical College of Virginia
Richmond, Virginia

- 2329 Lipman, V. C., Shurrager, P. S., & Abood, L. G. Effect of anticholinergic psychotomimetics on motor activity and body temperature. *Archives Internationales de Pharmacodynamie et de Therapie*, 146(1-2):174-191, 1963.

An attempt was made to establish a relationship between the hyperactivity induced in rats by a new group of psychotomimetic agents, the piperidinoglycolates, and their chemical constitution and psychotomimetic potency as previously evaluated in human subjects. A high correlation was found to exist between hyperactivity and psychotomimetic potency of *N*-methyl-3-piperidyl benzilate (NMPB), the agent most extensively used in these experiments. It was found that the hyperactivity induced by NMPB (5 mg/kg i.p.) was higher than predrug activity over an ambient temperature range of 0° to 42° C. However, activity decreased with increasing ambient temperature between 0° to 32° C. Colonic temperature rose with increasing ambient temperature, but no differences in colonic temperature were found between predrug and postdrug animals. From these results it was concluded that the piperidinoglycolates exerted an influence on

that section of the CNS involved in the regulatory control of temperature and motor activity. Several tranquilizers (phenothiazines and piperidine homologs of the piperidinoglycolates) successfully counteracted the hyperactivity response induced by NMPB. The ability of these tranquilizers to antagonize the hyperactivity of the piperidinoglycolates could, therefore, be used as a screening device for specific CNS depressants.

University of Illinois
Chicago, Illinois

2330 Bhagat, B. **The effect of adrenergic neurone blocking agents on the release and uptake of catecholamines by the rat heart.** Archives Internationales de Pharmacodynamie et de Therapie, 143(1-2):231-237, 1963.

This study compared the effects of adrenergic neurone blocking agents, 2,6-xylyl choline ether bromide (TM-10) and its β -methyl derivative (B-TM-10), with those of ganglionic blocking agents---hexamethonium and pentolinium---on uptake and release of noradrenaline in the rat heart. Male albino rats of the Holtzman strain (220 to 225 g in weight) were used in all experiments. Hexamethonium (10 mg/kg s.c.) or pentolinium (5 mg/kg s.c.), injected every 30 minutes, the last injection being 30 minutes before the animals were killed, increased the uptake of exogenous noradrenaline (1.5 mg/kg i.p. 1 hour before the animals were killed) and elevated the cardiac catecholamine content. The TM-10 (5 mg/kg i.v.) or B-TM-10 (5 mg/kg i.v.) administered 1.5 hours before noradrenaline (1.5 mg/kg i.p.) failed to influence the endogenous catecholamine levels or the uptake of the injected noradrenaline. Bretylium, TM-10, or guanethidine, all given at 5 mg/kg i.v. 1.5 hours before reserpine (1 mg/kg i.v.), reduced by the releasing of cardiac catecholamines by reserpine.

Department of Pharmacology and Toxicology
The University of Wisconsin Medical School
Madison, Wisconsin

2331 Lightowler, J. E. & MacLean, J. A. R. **Studies on some analogues of gamma-aminobutyric acid.** Archives Internationales de Pharmacodynamie et de Therapie, 145(1-2):233-242, 1963.

Results of the pharmacological screening of 30 derivatives or analogs of γ -aminobutyric acid (GABA) against the activity of bemegride,

pentylenetetrazol, and strychnine on the CNS are described. Albino Tuck mice (18 to 22 g) were used in all experiments. Methyl- γ -piperidinobutyrate (DF 494) at 7.5 mg/kg i.v., ethyl- γ -aminobutyrate HCl (DF 503) at 450 mg/kg i.v., γ -morpholinobutyric acid (DF 533) at 700 to 800 mg/kg i.v., and 2-pyrrolidone (DF 652) at 875 mg/kg and 1,750 mg/kg i.v. all showed antistrychnine activity, whereas GABA afforded no protection against strychnine (2 mg i.v.) convulsions. The GABA (250 to 1,000 mg/kg p.o.) and trimethadione (1,000 to 2,000 mg/kg p.o.) given 2 hours before bemegride (25 mg/kg s.c.) prevented convulsion and death due to bemegride. The γ -dimethylaminobutyramide (DF 570) at 250 mg/kg i.v. and trimethadione were active against the anticonvulsant action of pentylenetetrazol (2 mg i.v.) and bemegride (0.1 mg i.v.). None of the compounds tested, except GABA, had antihistamine or antiacetylcholine activity that was on the guinea-pig ileum.

Edinburgh Pharmaceutical Industries Ltd.
Edinburgh, Scotland

2332 Orcutt, J. A., Michaelson, S. M., & Prytherch, J. P. **The inhibition of nicotine-induced convulsions in the rat.** Archives Internationales de Pharmacodynamie et de Therapie, 146(1-2):238-244, 1963.

The responses of rats to the i.v. injection of nicotine were characterized in detail, and screening techniques for antinicotinic effects were selected. After the injection of nicotine (0.5 mg/kg i.v.), all of the rats went through stages of prostration, tremors, clonus, and clonic convulsions. Some of the animals progressed to more advanced stages of nicotine stimulation---opisthotonus, tonic flexion, tonic extension, and death. Prostration was unaffected by any of the antinicotinic test drugs. Phenobarbital (60 mg/kg p.o.) produced a 60% reduction in tremors when given $\frac{1}{2}$, 1, or 3 hours before nicotine. Caramiphen (220 mg/kg p.o.) produced 50%, 75%, and 100% reduction in clonic convulsion when given $\frac{1}{2}$, 1, or 3 hours, respectively, before nicotine injection. Phenobarbital (60 mg/kg p.o.), phenylacetylurea (280 mg/kg p.o.), and P-267 (60 mg/kg p.o.) also combatted clonic convulsions by 90%, 74%, and 63%, respectively. Tonic extension was reduced to zero incidence by caramiphen (220 mg/kg p.o.), phenylacetylurea (280 mg/kg p.o.), phenobarbital (60 mg/kg p.o.), and P-267 (60 mg/kg p.o.). Procaine

(220 mg/kg p.o.) and butacaine (170 mg/kg p.o.) reduced tonic extension to 10% incidence. Mortality was reduced to zero by all drugs tested.

The Norwich Pharmacal Company
Norwich, New York

- 2333 Marino, A., Parise, A. & Galdi, R.
Protective effect of mebutamate in the experimental cardiopathy induced by strophantin and psychological stress.
Archives Internationales de Pharmacodynamie et de Therapie, 145(1-2):276-287, 1963.

Lethal and electrocardiographic effects of κ -strophantin, as well as their interactions with psychological stress and/or mebutamate, were investigated in the guinea pig. Twenty-six adult male, guinea pigs (500 g) were divided into four groups as follows: Group 1 received κ -strophantin i.m. (0.3 mg/kg on the first day, 0.6 mg/kg on the fifth day, 0.9 mg/kg on the ninth day, and 1.2 mg/kg on the fourteenth day); Group 2 was conditioned to an avoidance situation, then forced into a conflict situation, and subjected to the strophantin treatment (same as Group 1); Group 3 was given mebutamate (20 mg/kg i.m.) 5 days before and during strophantin treatment; and Group 4 was forced into the conflict situation and then subjected to the treatment with mebutamate + strophantin. The results revealed that psychological stress exerted an evident and significant potentiation of strophantin cardiotoxicity. Mebutamate afforded significant protection against the cardiotoxic effects of strophantin, even when these effects were potentiated by psychological stress. The implications of these findings on the cardiac and psychic actions of mebutamate suggested the clinical applications of the drug in psychogenic cardiovascular diseases.

University of Naples
Naples, Italy

- 2334 Madan, B. R. **Some cardio-vascular actions of thioridazine hydrochloride.**
Archives Internationales de Pharmacodynamie et de Therapie, 144(3-4):299-309, 1963.

This report is based on the results obtained from an investigation of the effects thioridazine HCl on various circulatory parameters. Thioridazine HCl (5 and 10 mg/kg i.v.) administered to adult, mongrel anesthetized dogs (10 to 17 kg), produced hypotension,

bradycardia, direct femoral vasodilation, and prolongation of refractory period and conduction time (as measured by changes in the Q-T and P-Q intervals, respectively, of the ECG). The effect of the drug on the refractory period (lengthening of the Q-T intervals) was more marked than on conduction (lengthening of the P-Q intervals). Injection of thioridazine (100 μ g to 300 μ g) produced a 21.4% to 33.3% reduction in heart rate and 42.0% to 58.5% decrease in the amplitude of contraction in the perfused heart of the frog. Isolated rabbit's auricles in Locke's solution containing 1 mg% to 4 mg% of thioridazine showed a 6.4% to 21.5% reduction in the amplitude of contraction and 5.8% to 34.2% decrease in the sinus rate. Thioridazine (1 mg% to 4 mg%) also antagonized the hypertensive action of adrenaline (10 μ g% to 15 μ g%) in the rabbit auricles, but did not modify the positive chronotropic and ionotropic effects of adrenaline. Thioridazine produced a reversal of the ephedrine (5 mg/kg i.v.) effect in anesthetized dogs as well as a block of vagal stimulation. Prior treatment with thioridazine (1 mg% to 2 mg%) prevented the inhibitory action of acetylcholine (0.1 mg% to 0.2 mg%) on the isolated rabbit's auricles. These vagolytic-, sympatholytic-, and quinidine-like effects of thioridazine may contribute advantageously to its antiarrhythmic action.

Medical College
Bikaner, Rajasthan, India

- 2335 Chodera, A. **The influence of Marsilid on the temperature response in rats after morphine.** Archives Internationales de Pharmacodynamie et de Therapie, 144(3-4):362-369, 1963.

The influence of iproniazid, an MAO-inhibitor, on the temperature effects of morphine was investigated in rats. Female albino rats from a laboratory strain (150 to 250 g) were given morphine (10, 20, 30, or 40 mg/kg s.c.); a second group of rats from the same strain was given iproniazid (75 mg/kg i.p.) 20 hours before morphine. At 10 mg/kg, morphine alone produced an increase in temperature, whereas 20, 30, and 40 mg/kg of the drug produced a slight decrease during the first hour, followed by a temperature increase. In the iproniazid-morphine (10 mg/kg) group, a slight temperature decrease was recorded, and in the iproniazid-morphine (20, 30, or 40 mg/kg) groups, the temperature drop was more evident and persisted for more than 2 hours. Eight rats were given morphine (30 mg/kg/day

s.c.) and 10 rats were given this dose plus iproniazid (75 mg/kg i.p.) on every second day. Iproniazid inhibited the development of morphine tolerance (indicated by inhibition of the disappearance of temperature drop). Tolerance occurred immediately after withdrawal of iproniazid injections.

Medical Academy
Poznan, Poland

- 2336 De Salva, Salvatore. Effect of drugs on EST in various endocrine deficient states. Archives Internationales de Pharmacodynamie et de Therapie, 142(3-4):361-365, 1963.

This investigation was designed to measure the electroshock seizure threshold (EST) effects of drugs in male, Sprague--Dawley rats (4 weeks old) surgically treated to produce the following endocrine deficiencies: complete hypophysectomy (Hx), adeno-hypophysectomy (Antx), neurohypophysectomy (Postx), adrenalectomy (Adx), and thyroidectomy (Thyrx). It was found that EST was reduced in an order of descending magnitude by Adx, Hx, Antx, Postx, and Thyrx. The Hx, Antx, and Thyrx blocked the depressant action of phenobarbital (25 mg/kg s.c.) and diphenylhydantoin (50 mg/kg s.c.), and converted the depressive effect of the following drugs to excitation: serotonin (20 mg/kg s.c.), reserpine (1 mg/kg s.c.), ephedrine (10 mg/kg s.c.), and diphenhydramine (25 mg/kg s.c.). The increased excitement induced by LSD-25 (2 mg/kg s.c.) in intact rats was augmented under these endocrine deficient states. The Adx raised the depressant effects of the drugs, and Postx had only a minimal blocking or reversal effect. It was suggested that the drug activity reversal was related to thyroidectomy.

Biological Research Laboratory
Colgate-Palmolive Company
Somerset, New Jersey

- 2337 Hahn, F. & Oberdorf, A. Untersuchungen über die Wirkungsstärke der Analeptica Bemegrid, Pentetrazol und Pikrotoxin bei der Phenobarbital-Hydroxydion- und Ethinamatnarkose und über den Rexiproken. (Investigation of antilethal effects of the analeptics bemegride, pentetrazol, and picrotoxin against the narcoses of phenobarbital, hydroxydione, and ethinamate and their reciprocal antagonism.) Archives Internationales de Pharmacodynamie et de Therapie, 142(3-4):371-394, 1963.

The protective effects of the analeptics bemegride, pentylenetetrazol, and picrotoxin against lethal doses of the hypnotics phenobarbital, hydroxydione, and ethinamate, and the reciprocal antagonism of these compounds were studied in mice. The effectiveness of the analeptics against the hypnotics phenobarbital and hydroxydione increased in the order picrotoxin--pentylenetetrazol--bemegride. When the hypnotics were tested for protective effect against the analeptics, phenobarbital and hydroxydione were least effective against picrotoxin and most effective against bemegride. The three analeptics had no protective effect against ethinamate. When the reciprocal antagonism was tested, bemegride was least effective and picrotoxin most effective, but even the action of picrotoxin was very slight. The effectiveness of an analeptic against hypnotic poisoning seems to depend on the degree of mutual detoxification, which determines the amount of analeptic that can be administered safely.

Pharmacology Institute
University of Freiburg
Freiburg, Germany

- 2338 McKeon, W. B., Jr. Further studies on the antagonism of intravenous histamine in the guinea pig by piperidyl-alkylphenothiazines and chlorpromazine. Archives Internationales de Pharmacodynamie et de Therapie, 146(3-4):374-385, 1963.

A series of 48 piperidyl-alkylphenothiazines were tested as antagonists of the lethal effects of histamine in the guinea pig. Unfasted, albino guinea pigs (200 to 250 g) of either sex were given the antihistamines s.c. 30 minutes before the injection of 570 µg/kg i.v. of histamine diphosphate (about three times the LD₅₀). The dose (ED₅₀) protecting 50% of the animals was calculated from the dose-mortality (%) regression line, and the antihistaminic activities were compared with that of chlorpromazine. The compounds were classified

according to the substituents in the 2-position of the phenothiazine nucleus; the length of the alkylene bridge between the phenothiazine and piperidyl moieties; and the length of the alkylene chain on the terminal piperidyl carbon atom. From the results of the experiments, it appeared that antihistaminic activity depends on alkylene bridge length (decreasing order of activity: 3 carbon atoms > 2 carbon atoms > 4 carbon atoms) and/or the substituents in the 2-position of the phenothiazine nucleus (decreasing order of activity: hydrogen > acetyl > chloro > trifluoromethyl). The most potent compound of the entire series of drugs tested, 10-[3-(4-hydroxy-1-piperidyl)propyl] phenothiazine HCl, with an ED_{50} of 0.12 ± 0.02 mg/kg was about six times more active than chlorpromazine ($ED_{50} = 0.72 \pm 0.14$ mg/kg). The most active acetyl, chloro, and trifluoromethyl analogs were 10-[3-[4-(2-hydroxyethyl)-1-piperidyl]propyl]-2-acetylphenothiazine, 10-[3-[4-(2-hydroxyethyl)-1-piperidyl]propyl]-2-chlorophenothiazine HCl, and 10-[3-[4-hydroxy-1-piperidyl]propyl]-2-trifluoromethylphenothiazine HCl, with ED_{50} values of 0.23 ± 0.03 mg/kg, 0.20 ± 0.09 mg/kg, and 2.75 ± 0.87 mg/kg, respectively; these analogs were about 3.1, 3.6, and 0.3 as active as chlorpromazine, respectively.

Sterling-Winthrop Research Institute
Rensselaer, New York

2339 Sivadjian, J. Action de la chlorpromazine sur l'épilepsie expérimentale et sur la transpiration. (Action of chlorpromazine on experimental epilepsy and perspiration.) Archives Internationales de Pharmacodynamie et de Therapie, 143(3-4): 377-384, 1963.

The action of chlorpromazine was studied on epileptic seizures induced in the guinea pig by diethylaminophenoxyethane and on the rate of perspiration in mice. Chlorpromazine (25 mg/kg s.c.) did not suppress convulsions induced by 100 mg/kg diethylaminophenoxyethane; at 20 mg/kg s.c., chlorpromazine suppressed convulsions induced by 75 mg/kg s.c. of the convulsant. Chlorpromazine (25 mg/kg) produced an initial increase in perspiration, followed 30 minutes after injection by a great decrease in perspiration in mice.

Pasteur Institute
Paris, France

2340 McKeon, W. B. Antagonism of intravenous histamine in the guinea pig by piperidylalkylphenothiazines and chlorpromazine. Archives Internationales de Pharmacodynamie et de Therapie, 145(3-4): 396-404, 1963.

A series of 37 piperidyl-alkylphenothiazines, which were classified according to four general groups (those with no substitution on the 2-position of the basic phenothiazine nucleus and those having either a chloro, acetyl, or trifluoromethyl substituent), was tested as antagonists of histamine in the guinea pig. The phenothiazines were given s.c. as suspensions 30 minutes before injection of $570 \mu\text{g/kg}$ i.v. of histamine diphosphate (about 3 ID_{50} 's) to unfasted, albino guinea pigs (200 to 250 g). The dose protecting 50% of the animals (ED_{50}) was calculated from the dose-mortality (%) regression line and compared to that of chlorpromazine ($ED_{50} = 0.72 \pm 0.14$ mg/kg). The most active analog of the four groups of compounds tested, 10-[3-(4-hydroxy-1-piperidyl)propyl] phenothiazine HCl, ($ED_{50} = 0.12 \pm 0.02$ mg/kg), was about six times more potent than chlorpromazine. The most active chloro and acetyl analogs, 10-[3-(4-carbethoxy-1-piperidyl)propyl] chlorophenothiazine ($ED_{50} = 0.54 \pm 0.12$ mg/kg) and 10-[3-(4-hydroxyethyl-1-piperidyl)propyl] acetylphenothiazine ($ED_{50} = 0.53 \pm 0.10$ mg/kg), were about 1.3 and 1.4 times more potent, respectively, than chlorpromazine. Compounds having a 3 carbon alkylene chain elicited antihistaminic activity about 3 to 30 times more than that noted with the corresponding 2 carbon analogs. Dimethyl and diethyl substituted compounds were less active than their methyl and ethyl analogs; the methyl analog was more active.

Sterling-Winthrop Research Institute
Rensselaer, New York

2341 Hahn, F., Heidenreich, O., & Oberdorf, A. Über die temperatur- und blutzuckerwirkung von bemegrid, pentetrazol und pikrotoxin bei normalen und mit barbituraten vergifteten tieren. (On the temperature and blood sugar effects of bemegride, pentetrazol, and picrotoxin on normal and barbiturate-treated animals.) Archives Internationales de Pharmacodynamie et de Therapie, 142(2-4):395-424, 1963.

The effects of bemegride, pentylenetetrazol, and picrotoxin were studied on body temperatures and blood-sugar level in normal and barbiturate-treated mice and rabbits. In subconvulsive doses, bemegride, pentylenetetrazol, and picrotoxin lowered body

temperature in normal mice and rabbits; potency increased in the order bemegride—pentylenetetrazol—picrotoxin. In rabbits, hypothermia was accompanied by an increase in blood-sugar level, which was not pronounced with picrotoxin. In rabbits anesthetized with barbital or aprobarbital, the three analeptics raised the body temperature, which had been lowered by the action of the barbiturates, and induced arousal. In barbital-treated animals, pentylenetetrazol and bemegride, and occasionally picrotoxin, induced hyperthermia, which never exceeded 2° C. This hyperthermia occurred only if barbital was given in doses not larger than 300 mg/kg and if room temperature was high (24° C). The hyperthermia was considered to be an expression of a temporary lability in the body-heat-regulating system during drug-induced arousal.

University of Freiburg
Freiburg, Germany

2342 Plotnikoff, N., Keith, J., Heimann, M., Keith, W., & Perry C. Stimulant effects of tetrahydrocycloheptaquinoline derivatives. Archives Internationales de Pharmacodynamie et de Therapie, 146(3-4): 406-443, 1963.

The stimulant effects of cycloheptaquinoline derivatives were demonstrated by their potentiation effects on audiogenic seizures, amphetamine, pentylenetetrazol, and fighting responses in mice. The subconvulsive effects of nikethamide, α -amphetamine, and pentylene-tetrazol were markedly potentiated by MAS 795. At very low doses (1 to 8 mg/kg), imipramine also potentiated the effects of these drugs. The sedative effects of the compounds were observed in the depression of spontaneous motor activity and the prolongation of barbital sleeping time in mice. The MAS 795 was the most active agent. The MAS 795 had a sedative effect at relatively high doses (80 to 400 mg/kg), whereas at lower doses (10 to 80 mg/kg) a slight stimulant effect was observed. Several of the drugs also delayed the onset of sedation of tetrabenzazine in mice. The autonomic studies were carried out using dogs, rabbits, and cats. The aminocycloheptaquinolines were found to be cholinergic agents; at the same time, these same agents displayed weak anticholinergic effects at very low doses. The MAS 795 (1 mg/kg) potentiated the epinephrine response and cholinergic activity and, at doses of 0.25 and 0.1 mg/kg, it produced a distinct anticholinergic effect in dogs. The chlorocycloheptaquinolines appeared to reverse

their effects when used at very low doses. The cycloheptaquinolines also possessed anticholinergic effects.

The S. E. Massengill Company
Bristol, Tennessee

2343 Manchanda, S. K., Subberwal, U., Anand, B. K., & Bingh, Baldev. Effect of nialamide on the electroencephalographically recorded activity of the brain. Archives Internationales de Pharmacodynamie et de Therapie, 143(3-4):408-420, 1963.

To determine whether nialamide has any selective action on the activity of limbic regions in preference to neocortical regions, a study was carried out using 10 cats (2.5 to 3.5 kg) and 4 monkeys (3.5 to 5 kg). Bipolar electrodes were implanted in the hypothalamus, amygdala, hippocampus, anterior thalamus, cerebellum, and neocortex. Intracarotid or i.v. injections of 10 to 30 mg/kg nialamide were given to either anesthetized or unanesthetized animals. As a result of anesthesia, the characteristic sleep-like EEG records, were unaltered by injections of nialamide (20 to 30 mg/kg). The spontaneous low-voltage fast activity of unanesthetized animals changed to sleep-like patterns after nialamide. This was a nonspecific generalized response elicitable from all regions in which electrodes were implanted. The thresholds of stimulation for the after-discharge production from hippocampus, amygdala, hypothalamus, anterior thalamus, and cortex in unanesthetized preparations were increased after nialamide injections. Nialamide exerted an inhibitory influence on the excitability of the various regions of the brain, decreased the duration of after-discharges, and depressed its spread to other regions. Thus, nialamide depresses the electrical activity of the brain as a whole without selectively involving the limbic or the neocortical areas.

Department of Physiology
All-India Institute of Medical Sciences
New Delhi, India

2344 Mráz, M. The influence of chlorpromazine and pentamethonium on the carbohydrate metabolism and the resistance to trauma and to burn shock in rats. Archives Internationales de Pharmacodynamie et de Therapie, 141(3-4):423-433, 1963.

The effect of chlorpromazine and pentamethonium on carbohydrate metabolism was studied in rats subjected to traumatization in the

Noble--Collip drum and subjected to burn shock. Rats of both sexes weighing between 120 to 200 g were used in the experiments. Chlorpromazine (10 mg) and pentamethonium (20 mg) given 1 hour prior to the trauma improved the survival of the animals. The effect at lower doses was dependent upon the metabolic condition of the animals. The mortality rate was also reduced by chlorpromazine pretreatment in adrenalectomized rats. Neither chlorpromazine nor pentamethonium prevented the hyperglycemia due to trauma in rats in the Nobel--Collip drum. The hypoglycemic reaction after trauma in fasting animals was unaffected by pentamethonium (10 mg/kg i.m.), but chlorpromazine (5 mg/kg) fully prevented the development of hypoglycemia. Both agents failed to prevent a decrease in the liver glycogen down to minimal values. When the fasting animals were subjected to a slighter trauma, a large dose of chlorpromazine (10 mg/kg i.v.) sometimes caused hyperglycemia. When administered immediately after scalding or at the beginning of the trauma, chlorpromazine improved the course of shock. Pentamethonium had no effect on metabolic changes and did not influence resistance to trauma.

Faculty of General Medicine
Charles University
Prague, Czechoslovakia

2345 Mraz, M. & Triner, L. The effect of chlorpromazine on the metabolism of adrenalectomized rats. Archives Internationales de Pharmacodynamie et de Therapie, 141(3-4):434-442, 1963.

An investigation was conducted to determine the participation of the activation of the adrenals on the metabolic effect of chlorpromazine by comparing the influence of chlorpromazine and phenobarbital on the metabolism in normal and adrenalectomized Wistar rats (fasted for 24 hours). Chlorpromazine (10 mg/kg) and phenobarbital (100 mg/kg) was given i.v. Chlorpromazine caused hyperglycemia in normal animals, but the drug did not exhibit this effect in the adrenalectomized animals. No difference was found between the effect of chlorpromazine and phenobarbital. Chlorpromazine elicited a considerable increase of the liver glycogen in normal fasting animals but there was no increase in the adrenalectomized animals, even after 1 mg/kg of cortisone. Phenobarbital caused a higher rise in the content of glycogen in the muscle than chlorpromazine. Lipemia and ketonemia remained unchanged after drug administration.

The results suggest the importance of the adrenals as the origin of metabolic changes due to chlorpromazine.

Faculty of General Medicine
Charles University
Prague, Czechoslovakia

2346 Nilodijević, B. & Trajkov, T. Mechanism of ulcerogenic action of 5-hydroxytryptamine in rat's stomach. Archives Internationales de Pharmacodynamie et de Therapie, 143(3-4):442-445, 1963.

The mode of ulcerogenic action of 5HT was examined on 53 albino rats that were divided into four groups. One group served as controls so that the concentration of histamine and serotonin could be determined. The second group was given 5HT 20 mg/kg s.c., and the rats were killed 6 hours after the second injection. The third group was given antazoline 30 mg/kg i.p., and 5HT was given in the same doses as those given to the previous group. The fourth group was pretreated with iproniazid 100 mg/kg i.p., and 10 hours later 5HT was administered. The ulcer index and concentrations of histamine and serotonin were determined. Hemorrhagic erosion and ulceration were observed in the rat's stomach in the last three groups. The antihistamine drug antazoline, which is known to have almost no antiserotonin effect, reduced considerably the 5HT ulcers. The concentration of histamine was significantly diminished in gastric tissue of those rats treated only with 5HT. Iproniazid did not prevent 5HT ulcers; the concentration of serotonin in the gastric tissue was increased over that of the 5HT group. The ulcerogenic action of 5HT on the rat's stomach is the result of the histamine-liberating properties of this substance rather than by direct 5HT effect on the mucosa.

Department of Pharmacology
Medical Faculty
University of Skopje
Skopje, Yugoslavia

- 2347 Huidobro, F., Contreras, E., & Croxatto, R. **Studies on morphine.** III. **Action of metabolic precursors to serotonin and noradrenaline and related substances on the "abstinence syndrome" to morphine on white mice.** Archives Internationales de Pharmacodynamie et de Therapie, 146(3-4):444-454, 1963.

Adult male and female white mice (26 to 31 g in weight) were injected with nalorphine (10 mg/kg i.p.) following morphine-pellet implantation to induce an "abstinence syndrome." The modification of this syndrome by various substances in relation to syndrome intensity was investigated. Iproniazid (100 mg/kg i.p.) injected before nalorphine in control mice that were implanted with morphine reduced the intensity of the syndrome. Tryptophan administered in various ways and in various dosages always diminished the syndrome intensity, and 5HTP (12.5 to 150 mg/kg) and serotonin (150 mg/kg) induced an attenuation on the syndrome. These compounds were also employed in mice that were previously treated with iproniazid, LSD-25 (1 mg/kg), and ULM 491 (5 mg/kg). All three of these drugs reduced the intensity of the syndrome when serotonin was used; LSD-25 increased the intensity after tryptophan and 5HTP, and ULM 491 had little or no effect after tryptophan and 5HTP. The s.c. administration of 3-hydroxyanthranilic acid (240 mg/kg), anthranilic acid (600 mg/kg), shikimic acid (300 mg/kg), and *DL*-kineurenine (300 mg/kg) attenuated the intensity of the syndrome. The administration of DOPA (100 to 300 mg/kg), *DL*-tyrosine (900 mg/kg), and *DL*-phenylalanine (15 mg) decreased the intensity of the syndrome, and the same effect was observed after the administration of *DL*- α -methyldopa and *DL*- α -methyltyrosine (300 mg/kg).

Department of Pharmacology and
Department of Biochemistry
Catholic University of Chile
Santiago, Chile

- 2348 Esplin, Don W. & Rosenstein, Robert. **Analysis of spinal depressant actions of carbon dioxide and acetazolamide.** Archives Internationales de Pharmacodynamie et de Therapie, 143(3-4):498-513, 1963.

Tests were done at several levels of spinal-cord excitability, as determined by varying cord temperature, in order to investigate the general mechanisms of action of CO_2 and acetazolamide upon synaptic transmission. Both CO_2 and acetazolamide selectively depress the spinal monosynaptic response. The

CO_2 depresses the spinal monosynaptic spike to a greater extent than polysynaptic discharge of all concentrations studied (2.5% to 40%). In spite of the pronounced depressant effect, CO_2 is without effect on other aspects of synaptic transmission, such as synaptic recovery and PTP. Acetazolamide also is without effect on these aspects of synaptic transmission. Maximal depression of the monosynaptic response (about 30%) is seen with approximately 20 mg/kg of acetazolamide. The carbonic anhydrase inhibitor selectively depresses the monosynaptic response, but does not affect the other aspects of synaptic transmission. The mean effective doses for anticonvulsant effectiveness of carbon dioxide and acetazolamide in cats is 3.4% to 7.0% and 2.5 to 12.0 mg/kg, respectively.

Department of Pharmacology
University of Utah College of Medicine
Salt Lake City, Utah

- 2349 Deshpande, V. R., Sharma, M. L., Dashputra, P. G., Kherdikar, P. R., & Grewal, R. S. **Effect of chlorpromazine and prochlorperazine on Metrazol induced convulsions in frogs.** Archives Internationales de Pharmacodynamie et de Therapie, 141(3-4):525-531, 1963.

The effects of chlorpromazine and prochlorperazine on pentylenetetrazal-induced (10 mg/100 g) convulsions in frogs were studied in three sets of experiments with no stimulation, a fixed degree of stimulation, and continuous stimulation. All drugs were injected in the ventral lymph sac. The onset of convulsions is quicker and the percentage of frogs showing convulsion increased with the increase in dose of pentylenetetrazal. It also produced a loss of righting reflex and watering of the skin prior to the onset of convulsions. Both chlorpromazine and prochlorperazine in doses of 2.5 and 5 mg/100 g did not produce an effect, but doses of 10 and 20 mg/100 g produced tranquilization. Chlorpromazine and prochlorperazine (10 mg/100 g) significantly potentiate the pentylenetetrazal convulsions and its toxicity in frogs that are continuously stimulated.

Department of Pharmacology
Medical College
Nagpur, (Maharashtra) India

2350 Jacob, J. & Lafille, C. *Caractérisation et détection pharmacologiques des substances hallucinogènes. I. Activités hyperthermisantes chez le lapin. (Pharmacological detection and determination of properties of hallucinogenic drugs. I. Hyperthermic effects in the rabbit.)* Archives Internationales de Pharmacodynamie et de Therapie, 145(3-4):528-545, 1963.

Studies were performed to determine: (1) whether hallucinogenic drugs other than LSD, psilocybin, and mescaline produce hyperthermia in rabbits; (2) whether the hyperthermic effects differ from the known hyperthermic effects of pentylenetetrazol and dinitrophenol, which, under ordinary conditions, do not cause hallucinations in man; and (3) the possibility of using the hyperthermia reaction as a screening test for hallucinogenic drugs. Agents studied were lysergamide, psilocybin, mescaline, dimethyltryptamine, diethyltryptamine, two piperidyl diphenylglycolates (JB 318 and JB 336), nalorphine, phencyclidine, bromlysergamide, α -ethyltryptamine, and amphetamine. Rabbits were used in all experiments. All the hallucinogens increased temperature, except nalorphine. Effects increased with increasing doses for all agents except bromlysergamide and phencyclidine. The hyperthermic actions of the hallucinogens were indistinguishable from those of dinitrophenol. Correlations between chemical structure and ability to induce hallucinations and hyperthermia are discussed. It was concluded that, with due allowance for aberrant reactions such as that of nalorphine, the hyperthermia test is an effective screening agent for the evaluation of hallucinogenic properties.

Pasteur Institute
Paris, France

2351 Hanna, C., Upton, P. D., & Chambers, W. F. *Comparative effects of D-, L- amphetamine and L-phenyl-1-(piperidyl-2'-)-1-acetoxy-1-methane (R.P.-8228) in antagonizing barbiturate hypnosis.* Archives Internationales de Pharmacodynamie et de Therapie, 14(3-4):553-565, 1963.

The effects of *d*-amphetamine, *l*-amphetamine, and R.P.-8228 (2 to 6 mg/kg i.v.) in antagonizing barbiturate hypnosis are discussed. Three groups of cats were used. In animals immobilized with electrode implants in the rostral reticular formation of the midbrain, each of the drugs (4 mg/kg total dose) produced an alert EEG pattern of high frequency and low voltage that was not distinguishable from electrical stimulation. When 4 or 8

mg/kg of pentobarbital was given followed by 6 mg/kg of one of the stimulant drugs, a modified awake pattern was obtained. In the animals with chronically implanted electrodes and a depressant dose of 4 mg/kg of pentobarbital, the EEG record was one of high voltage and low frequency. High-frequency electrical stimulation produced an awake pattern, which was temporary. The animals appeared awake after 2 mg/kg of one of the stimulant drugs. When 4 mg/kg of R.P.-8228 or *l*-amphetamine was used, the cats became violent, but it was possible to give 6 mg/kg of *d*-amphetamine. All animals were agitated but unable to carry out coordinated and oriented movements. Following hypnosis, using 8 mg/kg of pentobarbital, it took 4 mg/kg of any one of the stimulant drugs to affect the EEG. The effect was one of increased frequency and a moderately high voltage. The stimulant action of these drugs was not effective against a total dose of 12 mg/kg of pentobarbital. The behavioral pattern following 8 mg/kg of pentobarbital was one of uncoordinated muscular activity. pentobarbital was one of uncoordinated muscular activity.

Department of Pharmacology
University of Arkansas Medical Center
Little Rock, Arkansas

2352 Dowling, C. & Hanna, Calvin. *Depressant effect of biperiden on the spontaneous EEG and the EEG-activation response.* Archives Internationales de Pharmacodynamie et de Therapie, 143(3-4):565-573, 1963.

The effect of biperiden on the spontaneous EEG and on the EEG activation response was compared with atropine and benztropine in 11 encéphale isolé cat preparations. The drugs were infused at cumulative dose levels of 0.25, 0.5, 1.0, 1.5, 10, 20, and 30 mg/kg, and the determination of the activation response was repeated between each dose. The degree of depression caused by these drugs was compared with the control values using the method of Riehl, Paul, and Unna. All three drugs produced similar effects on the spontaneous EEG at lower doses. A cumulative dose of 1.5 mg/kg of biperiden changed the resting rhythm of the spontaneous EEG to that of "neuronal synchronization." An alert pattern of fast frequency and low amplitude was exhibited after 10, 20, and 30 mg/kg. The threshold for changes in the activation response for all three drugs was 0.25 mg/kg. The marked increase in the threshold of the EEG alerting response to high-frequency stimulation of the reticular formation was

dose related, and the threshold dose for biperiden was between 0.25 and 0.5 mg/kg. At high doses (30 mg/kg) of biperiden (unlike atropine), the dissociative effect disappeared. Depression of several parameters of CNS activity occurred following a cumulative dose of 2 mg/kg of biperiden. An i.v. dose of 0.25 mg/kg of neostigmine bromide antagonized these depressant effects. No correlation was found between the effectiveness of these compounds in depressing the EEG activation response and in their peripheral anticholinergic potency.

Department of Pharmacology
University of Vermont
College of Medicine
Burlington, Vermont

- 2353** Del Castillo, J. & Nelson, T. E.
Further observations on the effect of carisoprodol upon the reticular control of spinal monosynaptic reflexes. Archives Internationales de Pharmacodynamie et de Therapie, 142(3-4):572-590, 1963.

The action of carisoprodol upon submaximal inhibition of the kneejerk by stimulation of the brain stem has been investigated in adult cats (2 to 4 kg in weight), spinal, decerebrate, or lightly anesthetized with pentobarbital. In decerebrate preparations in which a 100% inhibition of the knee jerk (K-J) was achieved by medullary stimulation, no changes were detected by carisoprodol, whereas a reduction of 25% to 40% K-J inhibition was converted to complete inhibition by 10 to 15 mg/kg of carisoprodol. The total cumulative dose of 3 mg/kg of carisoprodol (1 mg/kg + 2 mg/kg) increased the degree of inhibition from 30% to 70%. In both decerebrate and pentobarbital cats, a decrease in the degree of inhibition was observed with injections of mephenesin (5 mg/kg) or meprobamate (50 mg/kg). Carisoprodol (2 to 5 mg/kg) blocked facilitatory effects in highly excitable preparations (inhibitory stimulation was just under that required to oppose the potentiation caused by the stimulation of facilitatory areas), whereas the same dose failed to interfere with the facilitatory effects elicited from brain-stem sites in poorly excitable preparations (pentobarbital cats). In preparations undergoing reticular stimulation, eserine (0.3 mg/kg) potentiated spinal monosynaptic reflexes by its action on structures either identical, or closely related, to the brain-stem circuits involved in reticulospinal facilitation. The eserine-induced potentiation of the K-J in the spinal preparations was less marked than that produced in decerebrate animals.

Carisoprodol was a more powerful antagonist of eserine in decerebrate than in spinal preparations. This interaction between carisoprodol and eserine seemed to take place at a supraspinal level.

Department of Pharmacology
School of Medicine
San Juan, Puerto Rica

- 2354** Csötörtök, L., Perényi, L., Földes, I.
Correlation between structure and biological activity of 5-hydroxytryptamine (serotonin) and 4-hydroxytryptamine. Archives Internationales de Pharmacodynamie et de Therapie, 145(3-4):575-579, 1963.

Determination of the dissociation constants of 5HT and 4HT, and the results of measurements as compared with the biological activities of the two compounds were carried out using isolated rat uteri. The dissociation constants were determined spectrophotometrically. The results showed that the -OH group of 5HT and that of 4HT have nearly identical dissociation constants; correspondingly, the resonance energy changes are nearly equal to zero. The dissociation constant of the -NH₂ group of 5HT is 16 times higher than that of the 4HT. There is also a similar ratio between the biological activities of the two compounds.

National Institute for
Tuberculosis "Korányi"
Budapest 124, Hungary

- 2355** Richards, A. B., Hughes, F. W., & Forney, R. B.
Evaluation of anti-motion sickness drugs by component measurements of nystagmus in guinea pigs. Current Therapeutic Research, 5(11):587-593, 1963.

The evaluation of four anti-motion sickness drugs by three measurable components of caloric nystagmus in albino, male guinea pigs (300 to 400 g in weight) is presented. Predrug and postdrug controls were obtained on each animal, as well as in a group of untreated control animals. A visocorder was used to quantitate the three components of nystagmus. Structural formulas are presented for the four drugs. Cyclizine, meclizine, and cinnarizine were given at a dosage of 10 mg/kg. Dimenhydrinate was given 25 mg/kg, since it is used clinically at higher dosages than are the other compounds studied. The potency of these agents 1 hour after i.p. injection was cinnarizine > cyclizine >

meclizine > dimenhydrinate. After 2 hours, cyclizine and meclizine were reversed in order of potency.

Indiana University
School of Medicine
Indianapolis, Indiana

- 2356 Monroe, Russell R., Balis, George U., & Ebersberger, Ethel. **Anticonvulsant activity of alpha and beta chloralose in rats.** Current Therapeutic Research, 5(3):154-165, 1963.

The effect of glucochloraloses on various convulsive thresholds in female, albino Wistar rats was investigated. Convulsive thresholds were determined by using hexafluorodiethyl ether (HEE) (0.05 ml every 30 seconds), pentylenetetrazol (PTZ) (100 mg/kg i.p.), and electroshock (EST). Alpha chloralose (7.5 to 50 mg/kg) significantly raised the convulsive threshold of HFE and EST and, to a lesser extent, of PTZ. The anticonvulsant activity of alpha chloralose appeared as early as 15 minutes after drug administration, and reached its peak in about 1 hour. It is a quick-acting anticonvulsant that is rapidly inactivated. Alpha chloralose increased latency of convulsion and reduced the incidence of deaths. Although the anticonvulsant activity of beta chloralose occurred only at high doses (200 to 400 mg/kg) raised the convulsive threshold, increased the latency of convulsions, and gave protection against death. Alpha chloralose was more potent than phenobarbital on a dosage basis. The ED_{50} of alpha chloralose was 3.5 mg/kg, and the ED_{50} of phenobarbital was 8.4 mg/kg. The values of the protective indexes were almost identical. The effect of joint administration of these two drugs on the HFE thresholds suggests the existence of a synergism between the two.

The Psychiatric Institute
University of Maryland
School of Medicine
Baltimore, Maryland

- 2357 Mukasa, Hiroshi & Inanaga, Kazutoyo. **Study on the correlation between clinical and physiological responses to chlorpromazine.** Kurume Medical Journal, 10(1):21-28, 1963.

The possible relation between the clinical and physiological responses to chlorpromazine, as indicated by EEG and minor tremor (MT), was investigated in 10 male and 2 female patients selected at random from

hospitalized schizophrenics. During the first week of treatment, chlorpromazine was administered 100 mg/day and gradually increased by 100 mg/day every succeeding week. The usual dosage was between 200 and 600 mg/day. The EEG and MT recordings were done before medication, 1 week after the administration of chlorpromazine and afterwards once a week for 2 or 6 weeks. The frequency curves of EEG before treatment showed six cases with alpha-dominant pattern, four cases with no dominant peak, and two cases with the peak in the theta-dominant pattern. The frequency curves of EEG in six patients at the time of clinical improvement were altered from those observed before treatment. The frequency curves of six patients without clinical improvement at any time during treatment were relatively unchanged, in comparison with curves before treatment. Frequency curves of MT in all cases before medication showed four cases dominating at faster frequency bands, one case dominating at 9 to 10 c/s, and one case dominating at 8 to 9 c/s. After medication, the dominant peak was observed at 11 to 12 c/s. It was concluded that patients with favorable results had an atypical EEG and MT pattern before treatment, which could be altered to a normal pattern, and that those patients with unfavorable results had a rather typical pattern before treatment, which could be changed to an abnormal pattern by chlorpromazine therapy.

Kurume University
School of Medicine
Kurume-shi, Japan

- 2358 Khouw, Lip Boen, Burbridge, Thomas N., & Sutherland, V. C. **The inhibition of alcohol dehydrogenase. I. Kinetic Studies.** Biochimica et Biophysica Acta, 73:173-185, 1963.

Chlorpromazine was found to be a potent inhibitor (75% inhibition) at 500 μ M of horse-liver alcohol dehydrogenase. A 50% inhibition occurred at 28 μ M. Studies were carried out to determine if chlorpromazine interacted with known constituents of the molecule. It was found that neither the sulfhydryl groups nor the zinc in the molecule were affected by the drug. Kinetic investigations established that the inhibition was as follows: partial noncompetitive with respect to alcohol; partial uncoupling with respect to acetaldehyde; partial

coupling with respect to diphosphopyridine nucleotide; and partial noncompetitive with respect to reduced diphosphopyridine nucleotide.

Department of Pharmacology
University of California
San Francisco, California

- 2359 Nickel, J., Breyer, U., Claver, B., & Quadbeck, G. Zur Wirkung von Aminoethanol-Derivaten auf das Zentralnervensystem. (On the effect of aminoethanol derivatives on the central nervous system.) *Arzneimittel-Forschung*, 13:881-883, 1963.

The effects of procaine, deanol, and centrophenoxine were studied on glucose transport from the blood to the brain in mice (20 to 25 g in weight). Mice were given single i.p. injections of 100 mg/kg deanol, 46 mg/kg procaine, and 50 mg/kg centrophenoxine, and daily doses of 20 mg/kg p.o. centrophenoxine for 11 days. Thirty minutes after drug injection (in the case of semichronic doses, 30 minutes after the last dose), mice were given glucose labeled with C^{14} i.v., and the brains were examined for radioactivity. The effect of centrophenoxine was also tested on the transfer of Na^{24} , $H^{32}PO_4$, and acridin orange from blood to the brain in rats. The influence of centrophenoxine on the EEG of oxygen-deficient rats was determined. Centrophenoxine, as opposed to deanol and procaine, caused a marked increase in glucose transfer from the blood to cerebral tissues. This increase was not due to an increase in permeability of the blood-brain barrier. In simulated high-altitude EEG recordings, centrophenoxine exerted a definite protective action against oxygen deficiency.

Homburg University
Homburg/Saar, Germany

- 2360 Jílek, L. & Trojan, S. Ovlivnění odolnosti organismu proti oligémii a ischemii CNS během ontogeneze. (Influencing the resistance of the organism to oligemia and CNS ischemia during ontogenesis.) *Ceskoslovenska Pediatrie*, 18(1):28-32, 1963.

The effects of chlorpromazine, pentobarbital, and hyperglycemia induced by giving a 12% glucose solution were studied on experimentally induced oligemia and ischemia of the CNS in rats of various age groups (12 days old, 25 days old, and 4 to 6 months old). Oligemia was produced by tying off both carotid arteries for 8 hours. Ischemia

was produced by centrifugation at 10 gravities. Chlorpromazine was given i.p. in a dose of 10 mg/kg 90 minutes before ischemia and 30 minutes after tying off the carotids. Pentobarbital was given i.p. in doses of 20 mg/kg to 12-day-old rats and 40 mg/kg to 25-day-old and adult rats 15 minutes before ischemia and tying off the carotids. Hyperglycemia, chlorpromazine, and pentobarbital increased resistance to ischemia in all three age groups. Only glucose was effective against brain oligemia. The effects of chlorpromazine and pentobarbital were markedly dependent on the degree of maturity in the CNS. These drugs produced a favorable effect in 25-day-old rats but the reverse effect in 12-day-old and adult rats.

Comenius University
Prague, Czechoslovakia

- 2361 Skála, I. & Lamacová, V. Vliv benactyzinu na žaludční sekreci. (Effect of benactyzine on gastric secretion.) *Ceskoslovenska Gastroenterologie a Vyziva*, 17:271-274, 1963.

The effect of benactyzine on gastric secretion was studied in 10 patients, 9 males and 1 female, with hypersecretion and hyperacidity. Experiments were performed before breakfast. The stomach was manually aspirated, and the contents were evaluated at 15-minute intervals. Contents were not analyzed for the first two 15-minute periods. The next three samples (at 45, 60, and 75 minutes) were tested for basal secretion. The patients were then given 4 mg benactyzine s.c., and eight more samples were taken. Each sample was tested for volume (ml) and free and bound hydrochloric acid (mEq/l), and the output of free hydrochloric acid was calculated. Results showed that benactyzine reduced the volume of gastric secretion 40%, free acid 14%, total acidity 10%, and output of acid 50% in comparison with basal secretion.

Institute for Research on Human Nutrition
Prague, Czechoslovakia

- 2362 Way, E. Leong & Sutherland, V. C. Pharmacologically active brain substances and their relation to endocrine effects. *Anesthesiology*, 24:543-562, 1963.

Recent studies on the physiological significance of pharmacologically active substances in the CNS were discussed, with emphasis on neuroendocrine and pharmacologic aspects. The possible transmitter roles for

active substances in the brain, such as acetylcholine, norepinephrine, epinephrine, serotonin, Substance P (polypeptide), and γ -aminobutyric acid, were discussed. It was concluded that the hypothalamus exerts some regulatory control over the activity of the adenohypophyseal gland (containing ACTH and gonadotropic hormones). The manner in which the hypothalamus maintains this control is not known and must await development of a transmitter role for the pharmacologically active substances listed above.

University of California Medical Center
San Francisco, California

2363 Buggard, P. Un nouveau psychotrope stimulant et défatigant: La 5 phényl, 2 imino, 4 oxo oxazolidine. (A new psychotropic stimulant and anabolic agent: 5-phenyl-2-imino-4-oxo-oxazolidine.) *Thérapie*, 17:63-73, 1963.

The pharmacological properties of 5-phenyl-2-imino-4-oxo-oxazolidine in animals and man are described. The drug increases motor activity in mice, shows no sympathicomimetic peripheral action in dogs and rabbits, stimulates the reticular formation in rabbits, has a very low toxicity in mice and rats, and exerts an anabolic effect. In humans, the drug is devoid of toxicity, is not habit-forming, and has a slow, but prolonged, action. In high doses, the drug antagonizes neuroleptic effects and provokes slight desynchronization of the EEG, but no peripheral sympathicomimetic action. Low doses produce improvement in intellectual performances without inducing euphoria or affecting appetite or sleep. The drug is indicated for reactive depression or involutional depression with asthenia.

Mutual Protection Society of
French National Railroads
2 place des Peupliers
Paris, France

2364 Waskik, August. Zachowanie sie cislennia zylnego i srodczaszkowego w przebiegu leczenia schizofrenii chlorpromazyna. (The venous and intracranial CSF pressures in schizophrenic patients undergoing chlorpromazine therapy.) *Neurologia Neurochirurgia Psychiatria Polska*, 13:277-281, 1963.

The levels of venous-blood pressure and cerebrospinal fluid (CSF) pressure were measured before, 2 weeks after starting, and

after termination of chlorpromazine therapy in 63 schizophrenic patients. The CSF pressure dropped from the pretreatment level of 159.69 to 120.62 mm H₂O to an average of 120.64 mm H₂O. In eight patients, pretreatment levels of 120 and 175 mm H₂O dropped to 30 to 65 mm H₂O during treatment; these are the levels considered typical of intracranial hypotension. A simultaneous decrease in venous-blood pressure was present in these cases. No cytochemical changes were found on routine examination of the CSF. Neurasthenic complaints were commonly observed in patients with intracranial hypotension. There appeared to be a correlation between the decrease of venous-blood pressure and the decrease in intracranial pressure.

Academy of Medical Sciences
Wroclaw, Poland

2365 Glucose metabolism in the brain tissue of animals administered successively with beta-phenylisopropylmethylamine, and the influence of some psychotropic drugs on that metabolism. *Journal of the Keio Medical Society*, 40:41-47, 1963.

A study was made of the influence of chlorpromazine, imipramine, and tetrabenazine on glucose metabolism in the brains of guinea pigs given chronic doses of β -phenylisopropylmethylamine. Chronic administration of β -phenylisopropylmethylamine produced a distinctive metabolic pattern characterized by reduced aerobic glycolysis without impaired respiration. Brain cortex slices were examined for oxygen uptake and lactic acid production. No change in oxygen uptake occurred in brain tissue from guinea pigs treated with chlorpromazine and imipramine. In the tetrabenazine group, oxygen uptake decreased slightly from that measured in control groups (no drug and chronic β -phenylisopropylmethylamine alone). Chlorpromazine and tetrabenazine reversed the drop in lactic acid production caused by chronic β -phenylisopropylmethylamine administration. Imipramine produced a very slight increase in lactic acid production.

Keio University School of Medicine
Keio, Japan

2366 Petzold, H. & Kunath, U.

Histodemische reaktionen an der tierleber nach sensibilisierung und phenothiazin bzw. Kortikosteroidgabe. (Histochemical reactions in the animal liver following sensitization and phenothiazine or corticosteroid administration.) Allergie und Asthma, 9:65-72, 1963.

Histochemical reactions to sensitization with pig serum and phenothiazine or corticosteroid administration were studied in rabbit liver. Rabbits (2 to 3 months old) weighing 1.5 to 2.5 kg were treated as follows: (1) 8 rabbits sensitized with pig serum (0.5 ml/day serum the first week, 1.0 ml the second week, and 2.0 ml the third week i.v.); (2) 12 were given 0.15 mg/kg 6 α -methylprednisolone daily for 3 weeks; (3) 12 were given 2.5 mg/kg promethazine daily for 3 weeks; (4) 12 were given pig serum and 6 α -methylprednisolone (above schedules); (5) 12 were given pig serum and promethazine (above schedules); (6) 6 were given pig serum plus 0.15 mg/kg 6 α -methylprednisolone and 2.5 mg/kg promethazine daily for 3 weeks; and (7) 6 were given 0.15 mg/kg 6 α -methylprednisolone plus 0.1 mg/kg promethazine. Serum sensitization caused an increase in alkaline and acid tissue phosphatase in rabbit liver. When serum was given with 6 α -methylprednisolone or with promethazine, the phosphatases reacted to a much smaller degree. Decrease in the activity of cytochrome oxidase, succinodehydrase, and lipase was attributed to damage caused by drug administration.

University of Leipzig
Leipzig, Germany

2367 Betz, Donna & Ganong, William F.

Effect of chlorpromazine on pituitary-adrenal function in the dog. Acta Endocrinologica, 43:264-270, 1963.

The response of the adrenal cortex to psychic and surgical stress and to exogenous ACTH has been investigated in six mongrel dogs that were anesthetized by pentobarbital following the acute and chronic administration of chlorpromazine. The dogs were then given a single dose of 2.5 mg/kg of chlorpromazine i.v., which followed by 2.5 mg/kg given over a 30-minute period by constant infusion in 50 ml of isotonic saline. This administration did not decrease adrenal 17-hydroxycorticoid output significantly in stressed dogs; surgical hypophysectomy caused a marked drop in the same time interval. In dogs given 30 mg/kg/day, the rise in peripheral plasma 17-hydroxycorticoids following 2 hours of immobilization was

normal after 3 days of treatment, and the response to surgical stress and to 1 IU of ACTH was normal in dogs treated for 5 days. After hypophysectomy, 17-hydroxycorticoid output in chlorpromazine-treated dogs in response to 2-, 5-, and 10-milliunit doses of ACTH was slightly greater than normal, probably due to the mild adrenal hypertrophy produced by the drug. Chlorpromazine does not interfere with the determination of 17-hydroxycorticoids by the Silber-Porter method.

Department of Physiology
University of California Medical Center
San Francisco, California

2368 Menon, M. K. & Dandiya, P. C. Studies on central nervous system depressants. Part V. Pharmacological actions of *N*-acetyl, *N*-acetyl 3,4,5, trimethoxybenzamide. Indian Journal of Medical Research, 51(6):1037-1047, 1963.

A pharmacological investigation of *N*-acetyl-3,4,5-trimethoxybenzamide (*N*-acetyl TMB), a CNS depressant and hypotensive agent, was carried out. Three groups of five rats each were given i.p. injections of solvent, *N*-acetyl TMB at 20 mg/kg and 50 mg/kg, and chlorpromazine at 3 mg/kg, respectively, and were observed for spontaneous motor activity. The *N*-acetyl TMB reduced the spontaneous motor activity to a degree similar to that of chlorpromazine. Forty albino rats trained for choice discrimination were given chlorpromazine (3 mg/kg or 10 mg/kg) or *N*-acetyl TMB (20 mg/kg or 50 mg/kg). At the 50 mg/kg dose, anxiety to impending electric shock was greatly reduced by *N*-acetyl TMB, as well as by the 3 mg/kg dose of chlorpromazine. At 50 mg/kg i.v., *N*-acetyl TMB suppressed the fighting response in mice subjected to mild foot-shock. The 5HT content of brains of rats treated with *N*-acetyl TMB (50 mg/kg) was 0.418 μ g/g $\pm$ 0.043 μ g/g, and that of untreated rats was 0.421 μ g/g $\pm$ 0.06 μ g/g, which shows that *N*-acetyl TMB did not cause liberation of 5HT as reserpine does. The *N*-acetyl TMB (20 and 50 mg/kg) caused no analgesia in rats and did not potentiate analgesia due to morphine (0.8 mg/kg). The *N*-acetyl TMB (10 mg/kg) produced a hypotensive action in anesthetized dogs. Two phases of blood pressure fall were observed in the dog—an initial prompt fall and a secondary fall of blood pressure that was gradual and sustained. The prompt fall in blood pressure was due to

the central vagal effect of *N*-acetyl TMB and the secondary fall was mainly caused by the myocardial depressant action of the compound.

S.M.S. Medical College
Jaipur, India

- 2369 De Luca, P. L., Fabiani, F., & Vitale, S. Sugli effetti della thioridazina a livello delle gonadi: Ricerche istologiche sul testicolo e sulle ovaie de ratto. (Thioridazine effects on the Gonads. Histological observations in rats.) Rivista di Neurologia, 9(3):372-382, 1963.

The effect on the gonads of chronic thioridazine administration was studied histologically in Wistar rats. Twelve rats, six males and six females were used; two rats of each sex in this group served as controls. The remaining rats were given 10 mg/kg thioridazine i.p. daily for 20 days. Testicles and ovaries were then removed and immediately fixed in Carnoy solution, sectioned, and stained with hematoxylin, van Giesen, Brachet, and Hotchkiss--McManus stains. The testes showed hypotrophy of the seminiferous tubules, reduction in the number of cellular elements, and regressive phenomena in the germinative cells. The ovaries showed no evidence of histological modification. The mechanism by which testicular lesions were produced is discussed.

Psychiatric Hospital
Florence, Italy

- 2370 Li, H. Y., Chen, H., Chen, W. C., & Ting, K. S. Pharmacological studies of phenelzine on heart and coronary circulation. Scientia Sinica, 13:1455-1469, 1963.

The effects of phenelzine were investigated on coronary circulation, cardiac hemodynamics, coronary insufficiency, myocardial metabolism, noradrenaline content of the heart, and experimental atherosclerosis using guinea pigs, cats, dogs, rabbits, pigeons, and rats. Phenelzine concentration of 10^{-6} M exerted a significant inhibition on beating hearts with a concomitant increase of coronary flow in isolated guinea pig hearts, and 25 mg/kg produced the same effect on dog hearts in situ. However, chronic administration produced only a slight reduction in coronary blood flow and a slight augmentation in the vascular resistance. It did not potentiate the coronary vasodilating action

of noradrenaline and 5HT. Phenelzine (15 mg/kg) possessed a prophylactic action on pituitrin-induced hypoxia and isoproterenol necrosis of the myocardium of rabbits and guinea pigs. The monoamine oxidase and pyruvate oxidative enzyme systems were inhibited by phenelzine (10 mg/kg for 5 days) in heart homogenate of guinea pigs. Cardiac hemodynamic studies revealed that phenelzine (5 mg/kg) decreased the heart rate and dilated the peripheral vessels. The influence of phenelzine on the depletion of myocardial noradrenaline by tyramine (20 mg/kg), reserpine (1 to 2 mg/kg), and guanethidine (20 to 100 mg/kg) resulted in an augmentation of the noradrenaline-releasing action of tyramine, in a diminishing effect on reserpine-induced noradrenaline depletion, and in antagonism of the action of guanethidine. No therapeutic effect was demonstrated by phenelzine (10 mg/kg) on atherosclerosis in the aorta of pigeons.

Institute of Materia Medica
Academia Sinica
Shanghai, China

- 2371 Hrdina, P. & Kovalčík, V. K ovplyvneniu hemokoagulácie a účinku antikoagulancií inhibítormi monoamínooxydazy. (On blood coagulation changes and anticoagulant effect of monoamine oxidase inhibitors.) Casopis Lekaru Ceskych, 102: 574-579, 1963.

The effects of iproniazid, SKF 385B, methylene blue, and ephedrine were observed on blood coagulation and on the action of the anticoagulants ethyl biscoumacetate and phenylindandione. Coagulation tests were run in male Wistar rats (120 to 180 g in weight). Dosages were as follows: 50 and 100 mg/kg iproniazid p.o.; 50 mg/kg methylene blue; 5 mg/kg SKF 385B; 20 mg/kg ephedrine s.c.; 200 mg/kg ethyl biscoumacetate p.o.; and 50 mg/kg phenylindandione p.o. Thromboplastin tests were run in 12 rabbits. Six rabbits were given the three MAO inhibitors for 2 days, and six were given solvent. On the third day, each animal was given 1 ml/kg thromboplastin suspension i.v., and time of death due to thromboembolism was recorded. The MAO inhibitors iproniazid, SKF 385B, and methylene blue significantly potentiated the effects of the anticoagulants. Ephedrine lacked this effect. The potentiating effect of methylene blue on ethyl biscoumacetate was blocked by vitamin K. Iproniazid and methylene blue increased the prothrombin time slightly in normal rats, but SKF 385B

produced no change. In the thromboplastin test, iproniazid had no protective effect on the occurrence of lethal embolism.

Comenius University
Bratislava, Czechoslovakia

- 2372 Denisenko, P. P. & Pratushevich, Yu. M. 0 **trankviliziruysshchikh svoistvakh dvukh novykh tsentral'nykh kholinolitikov—metamazila i metildifatsila i vozmozhnykh tochkakh prilozheniya ikh deistviya.** (Tranquilizing properties of two new central cholinolytic preparations—metamisil and methyl-difacil—and possible application.) Zhurnal Nevropathologii i Psikiatrii imeni S.S. Korsakova, 63:582-590, 1963.

The tranquilizing properties of the cholinolytics metamisil (the diethylaminoisopropyl ester of benzylic acid) and methyl-difacil (the diethylaminoisopropyl ester of diphenylacetic acid) were studied in experiments on mice and rabbits and by clinical observations in children. The drugs inhibited the orienting reactions and prevented the development of rage, tension, and aggression in animals. Fifty children (9 to 15 years of age) were given the drugs prior to surgery. Metamisil was given in doses of 5µg/kg to 10µg/kg, and methyl-difacil was given in doses of 25µg/kg to 50µg/kg. The drugs abolished anxiety and tension in the children. Supplementary experiments were performed in children on the effect of the drugs on potentials evoked by stimulation of the cortex. Analysis of EEG patterns showed that the two drugs modified the energy of reactive potentials by different mechanisms of action. The influence of the drugs on nicotine- and arecoline-induced convulsions was also different. The drugs apparently affect different physiological pathways.

Academy of Medical Sciences
Leningrad, U.S.S.R.

- 2373 Tolmacheva, N. S. 0 **desensibiliziruyushchem deystvii mepazina.** (On the desensitizing action of mepazine.) Farmakologiya i Toksikologiya, 26:291-297, 1963.

Experiments were performed to determine the effect of mepazine on anaphylactic shock and on the Schwartzman phenomenon. In the first experiment, five guinea pigs were given 5 mg/kg mepazine i.m., 30 minutes

before i.p. injection of 0.5 ml horse serum; mepazine injections were continued for 15 days. Twenty-one days after injection of the first dose of horse serum, a second dose of 0.5 ml was injected. Mepazine had no effect on the development of sensitization, clinical appearance of anaphylactic shock, time of death, or survival. In the second experiment, 25 guinea pigs were given 0.5 ml horse serum. Twenty-one to 23 days later, a single injection of 0.5 to 4 mg/kg mepazine was given just prior to a second injection of horse serum. Injection of mepazine just before the second dose of serum weakened the anaphylactic reaction. In the third experiment, rabbits were given 25 mg/kg mepazine i.m., and the drug produced a desensitizing effect with regard to Schwartzman's phenomenon.

Institute of Pharmacology and Chemotherapy
Academy of Medical Sciences
Leningrad, U.S.S.R.

- 2374 Derevianko, L. D. 0 **vliyaniu nekotorykh lekarstvennykh veshchestv na obrazovaniye otaka izolirovannykh zadnikh konechnostey lyagushki.** (On the effect of some drugs on the production of edema of the isolated hind limbs in the frog.) Farmakologiya i Toksikologiya, 26:465-467, 1963.

The effects of Ringer's solution, 0.001%, 1%, and 25% calcium chloride, 0.01% chlorpromazine, 0.01% diphenhydramine, 0.01 unit ACTH, and 1%, 5%, and 10% tinctures of Lagochylus inebrians were tested on edema formation in isolated hindlimbs of frogs (Rana ridibunda Pall). Hindlimb preparations were made according to the method of Loewe—Trendelenburg in 260 frogs. The frogs were injected with 1 ml of test solution into the spinal lymphatic sac for 5 days. Pretreatment with chlorpromazine, diphenhydramine, ACTH, and Lagochylus extracts reduced considerably the edema formation. Pretreatment with the 10% solution of Lagochylus extract prevented edema formation to a much greater extent than did any of the other drugs tested.

Kuban Medical Institute
Kuban, U.S.S.R.

2375 Skorobogatov, V. I. Vliyaniye proizvodnykh fenotiazinovogo ryada na bioelektricheskuyu aktivnost' kory golovnog mozgo krolike. (Effect of derivatives of the phenothiazine series on the bio-electrical activity of the cerebral cortex in the rabbit.) *Farmakologiya i Toksikologiya*, 26:414-418, 1963.

Because of the dearth of information on the effect of phenothiazines on the EEG, the effects on the EEG produced by propazine, mepazine, chloracizine, and chlorpromazine were studied in rabbits. Fifteen rabbits were used in 27 experiments. The phenothiazines were given in doses of 2.5 mg/kg i.v. as 0.1% aqueous solutions. The EEG recordings were made from the sensorimotor region of the cerebral cortex and the brain stem before phenothiazine injection and 10 minutes after drug administration. In addition to measuring background activity, changes in EEG produced by a sound stimulus were also recorded. All four drugs, in doses of 2.5 mg/kg, evoked an increase in slow-wave amplitude and a suppression of the activation reaction in response to sound stimulus in the sensorimotor region of the cerebral cortex. The effect of drugs on bioelectrical activity in the cerebral cortex is related to the influence of the drugs on the reticular formation of the brain stem. The action of propazine and mepazine is weaker than that of chlorpromazine; the action of chloracizine is considerably stronger than that of chlorpromazine.

Central Scientific Research Institute of Medical Radiology
Leningrad, U.S.S.R.

2376 Grechishkin, L. L. Vliyaniye nekotorykh tsentral'nykh neyrotropnykh sredstv na motornuyu deyatel'nost' zheludka vne pishchevareniya. (The effect of certain central neurotropic agents on the extradigestive motor activity of the stomach.) *Farmakologiya i Toksikologiya*, 26:36-40, 1963.

The effect of a variety of centrally acting agents was studied on the continuous empty-stomach contractions in rabbits, using a chronic fistula procedure. Drugs given were: 0.07 to 0.1 mg/kg morphine and 0.05 mg/kg apomorphine; 7 to 10 mg/kg chlorpromazine, 5 to 6 mg/kg chloracizine, and 10 to 20 mg/kg meprobamate; 7 mg/kg hexobarbital sodium, 20 mg/kg thiopental sodium, 40 mg/kg amobarbital sodium, 500 mg/kg urethane, 120 mg/kg chloral hydrate, and 10 mg/kg pentylenetetrazol; and 2 to 5 mg/kg ephedrine, 2 to 4 mg/kg amphetamine,

0.025 mg/kg adrenaline, and 0.1 to 0.4 mg/kg galantamine. Drugs acting mainly on the subcortical formations of the CNS (barbiturates, pentylenetetrazol, morphine, and apomorphine) caused almost complete cessation of gastric activity. Drugs acting mainly on the cortex (urethane and chloral hydrate), and the tranquilizers chlorpromazine, chloracizine, and meprobamate failed to inhibit contractile movements. It was concluded that the subcortical formations play an important role in the contractile mechanism of the rabbit stomach.

Institute of Experimental Medicine
Academy of Medical Sciences
U.S.S.R.

2377 Dunaeva, V. F. & Ivanenko, E. F. Izmeneniye kolichestva sul'fgidril'nykh grupp i vosstanovlennogo glyutatsiona v golovnom mozgu u belykh myshey pri tormozhenii nervnoy deyatel'nosti, vyzvannom barbamilom, uretanom i medinalom. (Changes occurring in the amount of sulfhydryl group compounds and of reduced glutathione in the brain of albino mice following inhibition of nervous activity brought about by amytal sodium, urethane, and medinal administration.) *Farmakologiya i Toksikologiya*, 26:22-29, 1963.

Changes in the amount of sulfhydryl groups in brain proteins during inhibition of nervous activity caused by amobarbital, urethane, and barbitol were determined in the brains of mice killed at various intervals after drug injection. Corrections for sulfhydryl groups occurring from glutathione reduction were made by determining reduced glutathione in the same brain samples. Amobarbital was given s.c. in a dose of 0.1 mg/g; brains were removed after 4 to 7 minutes, 40 minutes, 2 hours, and 4 to 7 hours. After 4 to 7 minutes, no change in sulfhydryl groups occurred, but from 40 minutes to 2 hours, the number of sulfhydryl groups increased. Levels returned to normal after 4 to 7 hours. Urethane was given in doses of 1.2 mg/g (brains removed after 2 hours) and 2 mg/g (brains removed after 2 and 4 hours). Again, sulfhydryl groups in the brain proteins increased. Barbitol was given in doses of 0.24 mg/g (brain removed after 2 hours) and 0.4 mg/g (brain removed after 2 and 4 hours). Sulfhydryl groups increased, but raising the dosage to 0.4 mg/g caused no further intensification of sulfhydryl concentration.

Kharkov Pharmaceutical Institute
Kharkov, U.S.S.R.

- 2378 Lupachev, V. F. *K farmakologii apilaka. (Concerning pharmacology of the preparation apilacum.)* Farmakologiya i Toksikologiya, 26:333-338, 1963.

The pharmacology of apilacum, a preparation made from the natural secretion of the allotropic glands of bees, is described. Apilacum has low toxicity in white mice (27 to 34 g in weight) and white rats (150 to 260 g in weight), and is well tolerated in large doses. With repeated injection of small doses (0.5, 1, and 10 mg/kg), the drug has stimulating effects, expressed in an increase in motor activity and in weight of mice. Large doses (100 mg/kg and up) cause depression, decreased motor activity, and weight loss. Based on histological examination, the drug acts on some aspects of brain-cell metabolism. At doses of 100 mg/kg and higher, changes in cortical neurons and neurons of the subcortex and brain stem are observed. Apilacum distends blood vessels of the extremities and liver of frogs and of the heart and extremities of cats. The drug has hypotensive action, causing a rapid and permanent decrease in blood pressure. Injected parenterally, apilacum increases hemoglobin and erythrocyte contents of blood, but causes no substantial change in leucocyte count.

I. P. Pavlov Medical Institute
Ryazan, U.S.S.R.

- 2379 Markeva, I. V. *Zavisimost' reaktsii razvivayushchegosya organizma na aminazin ot gormonov kory nadpocheknikov. (Interdependence between the reaction of growing organism to aminazine and adrenal cortex hormones.)* Problemy Endokrinologii i Gormoneteraph, 9:3-7, 1963.

The relation between the reaction of growing animals to chlorpromazine and the content of adrenal cortex hormones was studied in newborn and adult rats. Adrenalectomized adult rats were less resistant to chlorpromazine than were intact adult rats. Restoration of initial resistance was achieved by administering glucocorticoids and mineral corticoids to the adrenalectomized adult rats; chlorpromazine differs from barbiturates, morphine, and reserpine in that resistance to the latter compounds is restored only by glucocorticoids. Newborn rats, whose adrenal cortex produces primarily mineral corticoids, were more resistant to chlorpromazine than were intact or adrenalectomized adult rats. When the rats are 3 weeks old, at which time the

hypothalamo--hypophyseal--adrenal system is fully developed, resistance to chlorpromazine decreases to the level seen in intact adult rats. Low resistance of newborn rats to barbiturates and morphine increases at 3 weeks of age to adult levels.

Leningrad Pediatric Medical Institute
Leningrad, U.S.S.R.

- 2380 Voevodina, O. N. *Vliyaniye amizila na protekaniye sekretornykh i situatsionnykh uslovykh reflektsov u sobak, podvergavshikhsya vozdeystviyu luchey rentgena. (The effect of amizyl on the course of secretory and situational conditioned reflexes in dogs exposed to X-rays.)* Farmakologiya i Toksikologiya, 26:410-414, 1963.

The effects of benactizine on conditioned reflex activity were studied in dogs previously subjected to whole-body irradiation with X-rays. Food conditioned reflexes to weak and strong stimuli, with differentiation at midexperiment, were established in one dog that had received 320 roentgens in 1955 and 40 roentgens in 1960. Five dogs were given 360, 320, 36, and 23 roentgens at various times. Two dogs received no X-irradiation and served as controls. Complex motor--situation conditioned reflexes were established in these dogs. Benactizine was given s.c., 15 minutes before experimentation, in doses of 0.01, 0.02, and 0.001 mg/kg. The drug altered the course of conditioned reflex activity for 3 to 20 days. These disturbances occurred at doses 100 to 1,000 times lower than those required to produce a comparable effect in unirradiated animals.

Academy of Medical Sciences
Leningrad, U.S.S.R.

- 2381 Huller, H., Schulz, E., & Scheler, W. *Zur Pharmakologie einer serie neuer benzilsäurederivate. I. Toxizität, analgetische aktivität und andere wirkungen auf das zentralnervensystem. (On the pharmacology of a series of new benzilic acid derivatives. I. Toxicity, analgesic activity and other effects on the central nervous system.)* Acta Biologica et Medica Germanica, 10:357-374, 1963.

The pharmacology of a series of 18 benzylic acid derivatives in mice and rabbits is reported. The following tests were performed: (1) acute toxicity in mice—LD₅₀'s determined by the s.c. route; (2)

analgesic activity—hot-plate test in mice and pulp-stimulation test in rabbits, and the Haffner tail-pinch test in mice; (3) rotating-rod test of muscular coordination; and (4) anticonvulsant effects—protective effect against pentylenetetrazol and electroshock seizures. In the analgesic test, morphine and aminopyrine served as standards. The most effective derivatives contained a branched alkyl group, a branched alkyl group with unsaturated linkages, or a straight alkyl with unsaturated linkages in the side chain of the OH group. Of the substituents on the COOH group, the dimethylaminoethyl chain was most effective. Combining the more effective compounds with morphine, caffeine, or a flavor derivative resulted in an additive analgesic effect. The compounds were potent anticonvulsants. They showed synergism with hexobarbital and methylpentynol and analeptic effects on respiration.

Pharmacology Institute
Ernst-Moritz-Arndt University
Greifswald, Germany

2382 Kusch, T. & Heinrich, I. Veranderungen im Kohlehydratstoffwechsel durch Chlorpromazin unter besonderer Berücksichtigung der Funktionen der Nebennieren. (Changes in carbohydrate metabolism due to chlorpromazine, with special consideration of adrenal function.) Acta Biologica et Medica Germanica, 10:317-322, 1963.

The effect of chlorpromazine on carbohydrate metabolism was studied in normal and adrenalectomized rats by measuring blood-sugar and liver-glycogen changes. The dynamics of blood-sugar and liver-glycogen levels were determined after glucose loading for extended periods of time before the experiment. Rats were fasted 18 hours preceding the experiments. Chlorpromazine was injected s.c. in various concentrations, with and without simultaneous administration of glucose. In normal rats, chlorpromazine increased both the blood-sugar and liver-glycogen levels at doses as low as 0.1 mg/100 g body weight, with and without glucose loading. No inhibition of sugar resorption from the intestines was observed. Chlorpromazine appears to promote the process of glucose formation. The drug did not increase glucose levels in adrenalectomized rats.

Friedrich-Schiller University
Jena, Germany

2383 Staib, A. H. Der Einfluss von Pharmaka mit zentraler Wirkungskomponente auf den Sauerstoffverbrauch der Karausche. (The influence of drugs with central active components on oxygen consumption in carp.) Acta Biologica et Medica Germanica, 10:333-342, 1963.

The influence of various centrally active drugs was studied on the oxygen consumption of carp (*Carassius vulgaris*). A method for examining pharmacological changes in oxygen consumption in fish is described. The fish were placed in an aquarium aerated at 50 mg oxygen/hour/100 g fish. Drugs were added to the water, and the following behavioral elements were measured: respiration rate and intensity, mobility, and spatial orientation. Drugs were given in the following concentrations: 5.0 g/l ethyl-urethane, 0.1 g/l phenobarbital, 0.05 g/l hexobarbital, 0.005 g/l chlorpromazine, 0.3 g/l caffeine, 0.01 g/l strychnine, and 10.0 g/l ethanol; the peripherally active drug 2,4-dinitrophenol (0.005 g/l) was given for comparison. Urethane, the barbiturates, and chlorpromazine reduced oxygen consumption, but 2,4-dinitrophenol, caffeine, strychnine, and ethanol increased it. The mechanisms of action for the drug effects on oxygen consumption are discussed. Basic differences in drug effects on the oxygen consumption of warm- and cold-blooded animals could not be traced.

Carl Gustav Carus Medical School
Dresden, Germany

2384 Wiezorek, W. D., Graupner, K. & Cieplik, U. Änderungen der Wirkungsstärke bei kombinierter Applikation von Chlorpromazin und blutzuckersenkenden Biguaniden. (Changes in the potency of chlorpromazine and hypoglycemic biguanides by combined administration.) Medicina Experimentalis, 8:237-241, 1963.

Changes in the LD₅₀'s of chlorpromazine and hypoglycemic biguanides resulting from combined administration were studied in male guinea pigs (300 to 500 g in weight). Standard LD₅₀'s are listed for promethazine and chlorpromazine i.p. and for buformin, phenformin, and metformin s.c. Changes in the LD₅₀ of chlorpromazine were measured when the phenothiazine was given 30 minutes before and 120 minutes after buformin and phenformin. Changes in the LD₅₀ of buformin were measured when the drug was given 120 minutes before and 30 minutes after chlorpromazine. When chlorpromazine was given first, toxicity was enhanced; when the biguanides were given

first, toxicity decreased. Findings are discussed in connection with the estimation of blood-glucose levels.

Karl Marx University
Leipzig, Germany

- 2385 Goschke, H., Burkard, W. P., Gey, K. F., & Pletscher, A. *Hemmung der Cholin oxydase in vivo durch Neuropharmaca.* (Inhibition of choline oxidase in vivo by neuropharmacological agents.) *Medicina Experimentalis*, 8:256-264, 1963.

To determine whether the clinical effects or side effects of iproniazid are based exclusively on MAO inhibition, or whether they are due partly to inactivation of another enzyme, such as choline oxidase, a study was done on the action of MAO inhibitors on rat-liver choline oxidase in vivo. The actions of the MAO inhibitors were compared with those of other neuropharmacological agents and ethionine. Male Wistar rats (180 to 250 g in weight), fasted 16 hours, were given a single i.p. injection of one of the 20 psychoactive drugs or ethionine and decapitated about 1 hour later. Choline oxidase activity was measured in liver tissue by Warburg manometry. Potent hydrazine MAO inhibitors only partially reduced choline oxidase activity. Reduction in MAO activity was 40 times greater. Potent nonhydrazine MAO inhibitors exerted no effect on choline oxidase activity. Amobarbital and ethionine caused a slight, but significant, effect on choline oxidase activity, but reserpine, amphetamine, and imipramine had no effect. Inhibition of choline oxidase activity has no effect on the therapeutic effect of the MAO inhibitors.

F. Hoffman-LaRoche & Co.
Basel, Switzerland

- 2386 Matthews, Richard J., Davanzo, John P., Collins, R. James, & Vander Brook, Milton J. *The pharmacology of chlorphenesin carbamate, a centrally active muscle relaxant.* *Archives Internationales de Pharmacodynamie et de Therapie*, 143(3-4):574-594, 1963.

The gross behavioral and neurological effects of chlorphenesin carbamate were studied in mice, rats and cats. The paralytic activity of chlorphenesin was compared with carisprodol, mephensin, mephensin carbamate, and meprobamate. The mean paralyzing dose of chlorphenesin was

151 mg/kg. Both chlorphenesin and meprobamate were less potent than the other agents but were longer acting. Chlorphenesin (50 mg/kg i.v.) increased the monosynaptic potential and decreased the polysynaptic potentials. The polysynaptic potentials were almost abolished by 150 mg/kg, but the monosynaptic potential was not depressed. Chlorphenesin 90 mg/kg abolished the electromyographic response. A depression of the maximal twitch response of the tibialis anticus muscle was produced by 100 mg/kg of the agent. Chlorphenesin was effective in antagonizing convulsions produced by strychnine and supramaximal electroshock, but was not antagonistic to pentylenetetrazol convulsions. Chlorphenesin (200 mg/kg) tended to produce slowing in the EEG, and the arousal response was delayed and shortened. The recruiting response of the diffuse thalamic projection system was depressed, whereas the alerting response mediated by the reticular activating system was relatively unaffected. The compound had no significant effect on autonomic or cardiovascular activity. Chlorphenesin was approximately five times more active than aspirin in alleviating pain produced by flexion of the silver nitrate-inflamed ankle joint of rats. It was ineffective as a diuretic and had no antihypertensive effect.

The Upjohn Company
Kalamazoo, Michigan

- 2387 Sackler, A. M., Weltman, A. S., & Sparber, S. B. *Effects of lysergic acid diethylamide on the total leukocytes and eosinophils of the female rat.* *Nature*, 199(4899):1194-1196, 1963.

This study was undertaken to determine the effects produced by prolonged administration of LSD-25 on adrenal activity by evaluating the alterations in total leukocyte, eosinophil, and differential blood-cell counts of 48 female Wistar rats, averaging 100 g in body weight and divided equally into three groups. Groups A and B were injected s.c. with 50 µg and 75 µg of LSD-25 dissolved in normal saline, and Group C control animals received an equivalent 1 ml dose of saline. To diminish tolerance effects, eight injections were administered over a 2-week period on alternate days. Doses of 50 µg induced a significant 34.4% decrease in the eosinophils of Group A rats as compared with control animals. The decrease in total leukocyte frequencies approached significance (0.09). Administration of 75 µg yielded a markedly significant decrease in leukocytic frequencies (0.01), with eosinophilic declines

slightly less than those observed in Group A rats (33.1%). In both groups, comparison of the differential data with the controls indicated a slight trend toward relative lymphopenia, eosinopenia, and neutrophilia. Although Group B data revealed a decline in the frequencies of the neutrophils, Group A results indicated little or no change in absolute neutrophil number. This study suggests a relationship of LSD-25 intoxication responses to schizophrenia that may go beyond mere psychomimetic similarities.

Laboratories for Therapeutic Research
Research Institute of the Brooklyn
College of Pharmacy
Long Island University
Brooklyn, New York

2388 Fuller, Renee. **Sexual changes in the male rat following chronic administration of reserpine.** *Nature*, 200(4906):585-586, 1963.

Reserpine (53 μ g/100 g/day) was administered to male rats to study the sexual changes following chronic administration of the drug. Six pairs of Long—Evans litter-mate sibs, 60 to 90 days old, were tested with a receptive female for 0.5 hour once a week after a 1-month familiarization with the testing enclosure. Eight weeks after reserpine administration, the average number of ejaculations decreased for the experimental group. Although the number of ejaculations decreased, the number of contacts required achievement of the first ejaculation increased 3 weeks after the drug. The drugged male mounted, with and without intromission, more frequently than did his control. Two latency measures—ejaculation and copulation—increased after reserpine. From these results it appears that chronic reserpine administration at low dosage has only limited effect on sexual arousal, but has a marked effect on ejaculation and on the amount of stimulation required for ejaculation.

Letchworth Village
New York State Department of Hygiene
Thiells, New York

See also: 2138, 2151, 2153, 2221, 2239, 2275, 2276, 2278, 2284, 2292, 2390, 2392, 2393, 2396, 2397

BIOCHEMISTRY

2389 Back, Kenneth C., Pinkerton, Mildred K., Cooper, Alan B., & Thomas, Anthony A. Absorption, distribution, and excretion of 1,1-dimethylhydrazine (UDMH). Toxicology and Applied Pharmacology, 5:401-413, 1963.

The absorption, distribution, and excretion of 1,1-dimethylhydrazine (UDMH) have been studied in rats, rabbits, cats, dogs, and monkeys by use of C^{14} -tracer and colorimetric methods. The animals were sacrificed 2, 4, 8, 12, 18, and 24 hours after injection of C^{14} UDMH, and portions of spleen, liver, midbrain and hindbrain, colon, kidney, heart, lung, and adrenal, weighting 100 to 500 mg, were removed, digested, agitated, and counted. Blood and urine chemical determinations were performed using trisodium pentacyanoamino ferrate. In rabbits given C^{14} -UDMH (50 mg/kg i.v.), the lowest concentrations of UDMH during the 24-hour period were found in the plasma. The UDMH was not, however, preferentially concentrated in any of the vital organs. Within the 24-hour period, 10% to 28% of the injected dose could be accounted for. Dogs and cats were given C^{14} -UDMH (50 mg/kg i.p.), and the blood concentrations by the colorimetric method were about one-half of the concentrations by the tracer technique. The urine levels, however, were about the same. In cats given untagged UDMH (10 and 50 mg/kg i.p.), rapid absorption occurred, and there was a marked correlation between urinary concentration and the dose (11% to 28% for 10 mg/kg and 29% to 48% for 50 mg/kg). There was also good correlation between plasma concentrations for 15 monkeys given 100 mg/kg UDMH on a time-dose basis. These monkeys showed 1-hour plasma levels averaging 70.4 μ g/ml, 2-hour levels of 52.9 μ g/ml, and 4-hour levels of 33.9 μ g/ml. The most sensitive indications of exposure to UDMH was the presence of the compound in the urine.

2390 Boissier, J. R. A new class of neuroleptics: Disubstituted N - N' piperazines. In: Society for the Study of Higher Nervous Activity. Proceedings of a Symposium on the Effects of Psychotropic Drugs on Higher Nervous Activity, Prague, 30 October-2 November 1961. Votava, Zdeněk, Horváth, Milan, & Vinař, Oldřich, eds. New York, MacMillan, 1963. p. 92-100, (Psychopharmacological methods.)

One of the disubstituted N - N' piperazines, N -(dimethoxy-3,4-phenethyl)- N' -(chloro-2-phenyl) piperazine (SD 218-06 or mephchlorazine), has been chosen, on the bases of its pharmacological effects and of methods used to assay the neuroleptic action, as one of the most active neuroleptics. During observation of general behavior of the mouse and rat, doses of 10 to 20 mg/kg i.p. produced a sedative, apathetic, and indifferent state to the environment. A similar sedative state occurred at p.o. doses of 20 to 500 mg/kg in the mouse and at 5 mg/animal in the dog. The soothing action in the rabbit was characterized by a relaxation of the neck muscle. In an open-field test on rats, rising doses of SD 218-06 (1, 2, 4, and 6 mg/kg i.p.) produced increased inhibition of activity. The ED_{50} 's were obtained with the rota-rod test, traction test, climbing test, and chimney test 30 minutes after injection. Administration of SD 218-06 (25 mg/kg i.p.) produced increased times of sleep in mice and rats given mebubarbital (50 and 25 mg/kg i.p., respectively). The SD 218-06 (10 mg/kg i.p.) removed hyperadrenergic activity in cats given morphine chlorhydrate (20 mg/kg s.c.). Hyperexcitation caused by iminodipropionitrile was completely abolished in mice after 5 mg/kg SD 218-06, and that due to cinnamyle transcarbamate was reduced greatly by 7 mg/kg SD 218-06.

Wright-Patterson Air Force Base
Dayton, Ohio

Institute of Pharmacology
Paris, France

2391 Keberle, H., Riess, W., & Hoffmann, K.
 Ueber den stereospezifischen
 metabolismus der optischen antipoden von
 α -phenyl- α -ethyl-glutarimid (Doriden). (On
 the stereo specific metabolism of the optical
 antipodes of α -phenyl- α -ethyl-glutarimide
 (Doriden).) Archives Internationales de
 Pharmacodynamie et de Therapie, 142(1-2):
 117-124, 1963.

In experiments in which racemic glutethimide was fed to dogs, four metabolites were isolated from the urine. The assumption that the metabolites, by virtue of their structural formulas, could be grouped in pairs and were derived specifically from the dextrorotatory and levorotatory forms of glutethimide was confirmed by feeding the pure *d* and *l* forms to dogs. The dogs were fed a total of 3 g of the isomers. The chemical procedure for separating the *d* and *l* forms is described. The *d* compound is hydroxylated in the glutarimide ring, and the *l* compound is hydroxylated in the ethyl side chain. Both hydroxylation products are, to a large extent, conjugated with glucuronic acid. Small quantities of these hydroxylation products are further metabolized, during which process the *d* compound loses water and the *l* compound loses acetaldehyde.

CIBA Corporation
 Basel, Switzerland

2392 Smyth, D., Pennington, G. W., &
 Jackson, N. Identification reactions
 of chlordiazepoxide ("Librium") and the
 product of acid hydrolysis 2-amino-4-chloro-
 benzophenone. Archives Internationales de
 Pharmacodynamie et de Therapie, 145(1-2):
 147-153, 1963.

Chlordiazepoxide and its hydrolyzed product, 2-amino-4-chlorobenzophenone, were subjected to a number of identification techniques, and data obtained by microcrystallography, chromatography, spectrophotometric analysis, and color tests are described. The microcrystalline forms of chlordiazepoxide were obtained with gold chloride, Martini's Reagent (potassium iodide--lead nitrate solution), Mayer's Reagent (potassium iodide--mercuric chloride solution), platinic chloride, and sodium iodide/platinic chloride; those of 2-amino-4-chlorobenzophenone were obtained only with the platinic chloride reagent. With the two solvent systems used for the paper chromatographic method, butanol--water--acetic acid (60, 25, 15) and amyl alcohol--water--acetic acid (50, 25, 25), both compounds were visualized under ultraviolet light as dark areas and

the *R_f* values of chlordiazepoxide were 0.88 and 0.91, respectively, whereas those for its hydrolyzed product were 0.21 and 0.26, respectively. Spectrophotometric analysis of the two compounds in 6 *N* hydrochloric acid revealed the maximal absorption points of chlordiazepoxide at 248 m μ and 308 m μ and points of minimal absorption at 220 m μ and 298 m μ in concentrations between 1:25,000 and 1:50,000. The hydrolyzed product showed points of maximal absorption at 261 m μ and of minimal absorption at 239 m μ . Differentiation between the two compounds was accomplished by a color test (Vitali's test) in which 0.1 ml of chlordiazepoxide solution was dried and 0.21 ml of fuming nitric acid was added to the residue. After evaporation to dryness, 0.5 ml of alcoholic potassium hydroxide was added to the dry residue. A brown--black coloration indicated chlordiazepoxide, but no color developed when the test was applied to the hydrolyzed product.

Department of Pharmacology
 Trinity College
 Dublin, Ireland

2393 Seiden, L. S. & Westley, J.
 Mechanism of iproniazid inhibition
 of brain monoamine oxidase. Archives Inter-
 nationales de Pharmacodynamie et de
 Therapie, 146(1-2):145-162, 1963.

This paper presents a mechanism for the inhibition of rat brain MAO by iproniazid. The MAO was prepared from rat-brain mitochondria, and its activity was measured spectrophotometrically. The reaction mixture consisted of deionized water, phosphate buffer (pH 7.4, final concentration 0.05 M), kynuramine, and enzyme. The blank contained all components except kynuramine. Addition of iproniazid (final concentration 10^{-4} M) to this reaction system resulted in inhibition after a definite delay period (about 16 minutes). This delay was repeated with the addition of a second aliquot of enzyme to the inhibited reaction. Incubation (about 30 minutes) of iproniazid with MAO resulted in the appearance of sufficient free isonicotinic acid to be detected polarographically. These results indicated that iproniazid was hydrolyzed to isopropylhydrazine and isonicotinic acid. The isopropylhydrazine caused the inactivation of the enzyme. Kynuramine and, presumably, other amine substrates of MAO were competitive substrates with iproniazid. In a kinetics study of MAO inhibition in which iproniazid was replaced by 10^{-6} M isopropylhydrazine,

the inhibition of MAO was of the same type as iproniazid-derived inhibition except for the absence of the delay phenomenon.

University of Chicago
Chicago, Illinois

- 2394 Smyth, D. & Pennington, G. W. The detection and excretion of chlordiazepoxide ('Librium') in human plasma and urine. Archives Internationales de Pharmacodynamie et de Therapie, 145(1-2):154-165, 1963.

A study was made of the qualitative and quantitative detection of chlordiazepoxide after the administration of an oral 100-mg dose to nine human volunteers. Qualitative examination was carried out using micro-crystalline, chromatographic, and spectrophotometric techniques. Unchanged chlordiazepoxide was present in both plasma and urine, and it seemed that at least one urinary metabolite was present. Quantitative examination revealed a slow rise in the chlordiazepoxide concentration of the plasma following administration. The drug persisted in the plasma for a relatively long period of time (72 hours or 7 days) after a single dose. The maximum excretion of the drug via the kidney was observed 24 to 30 hours following administration, but small amounts of chlordiazepoxide continued to be excreted over a long time period. The total amount excreted during the 48-hour period after administration was found to be less than 1%. These results indicated that chlordiazepoxide was slowly metabolized, and the persistence of the drug in the plasma was of importance in view of the prolonged courses of treatment with chlordiazepoxide in psychiatric practice.

Department of Pharmacology
Trinity College
Dublin, Ireland

- 2395 Ewaldsson, Bertil. Autoradiographic studies on the distribution of H^3 -meprobamate in the body. Archives Internationales de Pharmacodynamie et de Therapie, 142(1-2):163-169, 1963.

This investigation was undertaken to obtain a general picture of the distribution of meprobamate in mice by labeling the meprobamate with tritium gas and examining it autoradiographically after p.o. and i.v. administration. Pregnant and nonpregnant white mice (20 to 35 g in weight) were given

the labeled meprobamate at doses of 0.2 to 0.5 mg (corresponding to 460 μ C/mouse to 675 μ C/mouse). An even distribution of the meprobamate in the tissues was observed 4 hours after the injection. Up to 4 hours after injection, the hypophysis showed an uptake of radioactivity about twice as high as the uptake in the brain, and the liver had a higher content than the blood. One hour after injection, the level of activity in the fetus was higher than in the maternal tissue, but this activity decreased within 4 hours. Most of the meprobamate was excreted via the kidney within 24 hours. It was not possible to demonstrate any specific localization in the brain that could be related to meprobamate's mode of action.

Department of Pharmacology
Royal Veterinary College
Stockholm, Sweden

- 2396 Harris, L. S., Clarke, R. L., & Demibinski, J. R. α -Benzyltetrahydrofurfurylamines—a new series of psychomotor stimulants. III. The pharmacology of D-threo α -benzyl-N-ethyltetrahydrofurfurylamine (zylofuramine). Archives Internationales de Pharmacodynamie et de Therapie, 146(3-4):392-405, 1963.

Some pharmacological properties of D-threo- α -benzyl-N-ethyltetrahydrofurfurylamine (zylofuramine) have been described. Zylofuramine (2 to 128 mg/kg p.o.) was more potent than D-amphetamine, at the same dose, as a psychomotor stimulant in male albino mice (18 to 20 g in weight) and readily reversed the depression produced by chlorpromazine (3 mg/kg i.p.). Zylofuramine (3.0 to 120 mg/kg) produced a stimulation that was unaccompanied by the autonomic stimulation and hyperexcitability seen with amphetamine at comparable doses. In overt behavior studies in cats and monkeys, zylofuramine was less potent than D-amphetamine as a CNS stimulant, but it was active over a wider dosage range (2.0 to 32.0 mg/kg p.o. for zylofuramine and 0.5 to 2.0 mg/kg for amphetamine). Little cardiovascular activity was shown by zylofuramine in anesthetized dogs and cats and unanesthetized dogs, and the compound appeared to be less than one-tenth as active as amphetamine. Electrocardiac and behavioral arousal was seen in unanesthetized and unrestrained cats at 2.0 to 8.0 mg/kg i.p. zylofuramine, and electrocardiac alerting alone was seen at 0.5 and 1.0 mg/kg. Zylofuramine had little effect on appetite and did not block the monoamine oxidase or β -hydroxylase enzyme systems. The compound had a low acute toxicity at dosages of

32 mg/kg i.v. and 475 mg/kg p.o. and did not show an increase in toxicity on aggregated mice. Zylfuramine had no effect on body temperature, whereas *D*-amphetamine produced significant hypothermia.

Sterling-Winthrop Research Institute
Rensselaer, New York

2397 Deltour, G., Mercier, J., Charlier, R., Frost, M., Binon, F., & Etzensperger, P. Influence du remplacement du radical phényle par le radical propargyle sur les effets toxicomanogènes de la phénéthyl-1-phényl-4 propionoxy-4-pipéridine. (Influence of the replacement of the phenyl radical by the propargyl radical on the addiction-producing effects of phenethyl-1-phenyl-4-propionoxy-4-piperidine. Archives Internationales de Pharmacodynamie et de Therapie, 142(3-4):493-509, 1963.

Tolerance and habituation to 1-phenethyl-4-phenyl-4-propionoxy-4-piperidine (L 3190) and its analog 1-phenethyl-1(propion-2-yl)-4-propionoxy-4-piperidine (L 2909) were studied in a variety of animal experiments. Tolerance to the antitussive effects of the drugs was studied in cats and guinea pigs. Tolerance to the analgesic effects was studied in mice. The effects of withdrawal of the drugs after chronic administration were studied in rats and dogs. The effect of chronic administration on learning behavior was studied in rats. Monkeys were used to determine the dose of the drugs required to produce psychomotor disturbance without excessively affecting general behavior and to determine the ability of the drugs to suppress the symptoms of morphine withdrawal. Replacement of the 4-phenyl radical of L 3190 with a propargyl radical, forming L 2909, caused a considerable quantitative change in pharmacological and toxicological properties, particularly with regard to tolerance to analgesic and antitussive action. Habituation to L 2909 was less severe, and both tolerance and habituation developed much more slowly.

Belgian Nitrogen and
Chemical Products Company
Brussels, Belgium

2398 Ramos, A. O., Chapman, L. F., Ramos, L., & Zileli, T. Neurokinin from cerebrospinal fluid. III. Reciprocal actions with some drugs. Archives Internationales de Pharmacodynamie et de Therapie, 146(3-4):511-516, 1963.

The influence of some drugs on the action of neurokinin obtained from human cerebrospinal fluid and on bradykinin from ox blood was

studied. The isolated rat duodenum in Ringer-Locke solution and intact rats (180 to 250 g in weight), anesthetized with sodium pentobarbital, (130 mg/kg i.p.), were used for the experiments. Lysergic acid diethylamide (LSD) at 25 µg/kg and 50 µg/kg and lysergic acid butanolamide (UML) at 250 µg/kg to 1,000 µg/kg enhanced the hypotensive effects of neurokinin (12, 18, and 30 mg) in the rat. The LSD (0.01 µg/kg to 0.03 µg/kg) and UML (1.0 µg/ml to 1.5 µg/ml) enhanced the relaxation of the duodenum due to neurokinin (0.33 to 2.00 mg/ml). Sodium salicylate (150 to 200 mg/kg) and hydrocortisone (50 to 100 mg/kg) antagonized the effects of neurokinin (12 to 20 mg) on the rat blood pressure and duodenum, whereas the bradykinin effects were not affected by these drugs.

University of Sao Paulo
Sao Paulo, Brazil

2399 Nano, G. M., Sancin, P., & Tappi, G. Über die Persulfatoxydation der 10-(Dialkylamino-alkyl)-Phenothiazine. (On the persulfate oxidation of 10-[dialkylaminoalkyl]-phenothiazines.) Pharmaceutica Acta Helvetiae, 38:623-633, 1963.

The separation and identification of the persulfate oxidation products of various 10-(dialkylaminoalkyl)-phenothiazines are described. Differences in the oxidation behavior of the compounds appear to be due to the distance between nitrogen atoms. If there are two carbon atoms between the two nitrogen atoms, the chain is split, yielding aldehydes (formaldehyde, acetaldehyde) and a dialkylamine; the nucleus is converted into phenothiazone-3 and unidentified quinones. If there are three carbon atoms between the two nitrogen atoms, the compounds yield the corresponding sulfoxides and do not split at the dialkylaminoalkyl side chain. The sulfoxides can yield phenolic compounds by the Smiles' rearrangement.

University of Torino
Torino, Italy

2400 Stainier, C., Bosly, J., Dutrieux, Fr., & Stainier, R. Influence des substituants sur la stabilité des barbituriques en milieu alcalin. (Influence of substituents on the stability of barbiturate in an alkaline medium.) Pharmaceutica Acta Helvetiae, 38:587-595, 1963.

The degradation of various barbiturates was studied in alkaline medium at room temperature. In the course of analysis

of a mixture of barbiturates, *N*-methylphenobarbital was observed to decompose rapidly in the presence of $N Na OH$, but phenobarbital did not. Hexobarbital, with two methyl radicals, one on a nitrogen atom and the other on C 5, also showed this rapid decomposition in alkaline medium. The behavior of three other nitrogen--methyl derivatives, *N*-methylbromoallylisopropylbarbituric acid, was observed in $N Na OH$ medium, and these compounds showed a comparable rapid decomposition. When the trimethyl derivative, *N*-methyldiemethylbarbituric acid, was studied in $N Na OH$ medium, decomposition was so rapid that spectrophotometric examination was almost impossible. It was concluded that the addition of methyl groups and the presence of a methyl and a phenyl group both cause increased sensitivity of barbiturates to decomposition in alkaline medium.

University of Liege
Liege, Belgium

2401 Bruno, A., Bozzi, R., Allegranza, A., & De Vito, C. *L'eliminazione dei principali metaboliti urinari della serotonina, dopamina, noradrenalina, adrenalina durante trattamento con reserpina e con clorpromazina in soggetti schizofrenici. Correlazioni clinico-biologiche.* (The elimination of the principal urinary metabolites of serotonin, dopamine norepinephrine, and epinephrine in schizophrenic subjects under treatment with reserpine and chlorpromazine.) *Rivista di Patologia Nervosa e Mentale*, 84:451-492, 1963.

The urinary elimination of 5HIAA, the principle metabolite of 5HT; of homovanillic acid (HVA), the principle metabolite of dopamine; and of vanilmandelic acid (VMA), the principle metabolite of epinephrine and norepinephrine was studied in 18 male schizophrenics being treated with chlorpromazine and reserpine. An attempt was made to correlate changes in level of these metabolites and in the clinical effects (both side effects and therapeutic effects) produced by the drugs. Of the 18 patients, 9 received reserpine and 9 received chlorpromazine. Reserpine was given in doses of 3 to 12 mg (average daily dose, 7.98 mg; average total dose, 117 mg), and chlorpromazine in doses of 75 to 1,200 mg (average daily dose, 545.92 mg; average total dose, 9,345 mg). Both reserpine and chlorpromazine increased elimination of 5HIAA and HVA and decreased VMA. Correlations were noted between decreased VMA and vascular side effects, increased HVA and extrapyramidal

effects, and increased 5HIAA and gastrointestinal and respiratory disturbances. No correlation was noted between changes in metabolite excretion and changes in psychic condition.

Provincial Psychiatric Institute
Milan, Italy

2402 Schmid, E., Hoppe, E., Meythaler, Chr., Jr., & Zicha, L.
Dunnschichtchromatographische trennungen antidepressiv wirksamer Psychopharmaka. (Thin-layer chromatographic separation of antidepressive psychotropic drugs.) *Arzneimittel-Forschung*, 13(11):969-972, 1963.

Methods for the thin-layer chromatographic separation and identification of 12 antidepressant drugs in biological media are discussed. The following drugs were studied: isoniazid, iproniazid, nialamide, 1-pivaloyl-2-benzylhydrazine, isocarboxazid, phenelzine, pheniprazine, etryptamine, tranlylcypromine, imipramine, desmethylinipramine, and amitriptyline. The drugs were separated using silica gel-G, thin-layer chromatography. Of the many solvent extraction systems tested, the following were most effective: (1) chloroform:methanol (8:2); (2) chloroform:acetone:diethylamine (5:4:1); and (3) cyclohexane:chloroform:diethylamine (4:5:1). Color reactions were performed with 40% H_2PO_4 , 6N H_2SO_4 , Folin-Ciocalteu reagent, and a 5% solution of phosphomolybdic acid in ethanol with posttreatment of the thin-layer plate with ammonia fumes. Color reactions were measured in daylight and by ultraviolet light. Nialamide, imipramine, and amitriptyline were extracted quantitatively from gastric juice and determined chromatographically using the methods described.

Erlangen-Nürnberg University
Erlangen-Nürnberg, Germany

2403 Rýznar, J., Uhlíř, F., & Grumilík, R.
Stanovení chlorpromazinu v moči a možnosti jeho použití v praxi. (The determination of chlorpromazine in the urine and its possible use in practice.) *Ceskoslovenska Psychiatrie*, 59:241-245, 1963.

The color reaction tests of Neve (1958) and of Forrest (1961), and Forrest's universal test for the detection of phenothiazines in urine were used to determine the presence of chlorpromazine in 496 patients receiving

chlorpromazine therapy. The urines of 133 patients who were not receiving phenothiazines were also tested to determine the incidence of false positives. Of the 629 patients studied, 24 were children, 291 were adult males, and 314 were adult females; the age range was 10 to 85 years, with the majority between 31 and 55 years. In the 496 patients receiving chlorpromazine therapy, daily dosage ranged from 25 to 800 mg, with an average dose of 75 to 300 mg/day in 373 patients. The urine of each patient was used in four tests: Neve's nitrite test, Neve's nitric acid test, the Forrest test, and Forrest's universal test. All four tests were very sensitive; Forrest's universal test had the highest sensitivity. With doses of over 100 mg/day, 92% of the chlorpromazine-treated patients gave positive reactions. When doses were over 300 mg/day, 100% gave positive reactions. Age of the patient did not influence the values obtained. The tests are recommended for both inpatient and outpatient practice to determine whether the prescribed dose of phenothiazine is being taken. The tests can also be used in the differential diagnosis of poisoning by unknown substances.

Psychiatric Hospital
Opava, Czechoslovakia

2404 Sykulski, Jerzy. *Badania w grupie pochodnych fenotiazyny i otrzymywanie 10-(3'-dwumetyloaminopropyl)-3-chloro-fenotiazyny. (Studies on phenothiazine derivatives and on the production of 10-(3'-dimethylaminopropyl)-3-chlorphenothiazine.)* Acta Poloniar Pharmaceutica, 20(6):419-422, 1963.

The synthesis of 10-(3'-dimethylaminopropyl)-3-chlorphenothiazine HCl is described. The syntheses of each intermediate compound are also described. Paper chromatographic analysis of the substance derived in the last step of the procedure showed three products with different melting points: (1) 3-chlorphenothiazine; (2) 10-(3'-dimethylaminopropyl)-3-chlorphenothiazine; and (3) chlorpromazine.

Academy of Medical Sciences
Lodz, Poland

2405 Johannesson, Torkell & Schou, Jens. *Morphine and normorphine in the brains of rats given identically analgaesic doses of morphine, codeine or normorphine.* Acta Pharmacologica et Toxicologica, 20(2): 165-173, 1963.

An analgesimetric procedure was employed on rats to compare the analgesic potencies of morphine, codeine, and normorphine. Adult male, albino rats of a single strain (140 to 230 g in weight) were used. Nine groups of rats 30 to 50 animals in each group, were given i.p. injections of morphine (2.5, 5.0, or 10.0 mg/kg), codeine (10, 20, or 40 mg/kg), or normorphine (10, 20, or 40 mg/kg), and the analgesic effect was determined 30 minutes later. Analgesia occurred when three stimuli (square wave pulses of 3 volts applied to the tail for 20 milliseconds), which were more than the number of stimuli given to provoke a squeak in the control test, could be given without response. Morphine was found to be 3.3 and 6 times more potent than codeine and normorphine, respectively. Doses of the three drugs that produced 37.5% and 70% analgesia (5 and 8.5 mg/kg morphine, 6 and 30 mg/kg codeine, and 28 and 51 mg/kg morphine) were used to determine the morphine and normorphine levels in the brain. The concentrations of morphine in the brain were in the same range whether analgesia was produced by morphine or codeine (0.19 µg/g to 24 µg/g). The concentration of normorphine was 4 to 5 times higher than the concentration of morphine. These results indicate that codeine was o-demethylated into morphine before exerting its analgesic effect and that morphine analgesia was not due to normorphine.

University of Copenhagen
Copenhagen, Denmark

See also: 2151, 2304, 2309, 2331, 2340, 2354, 2365

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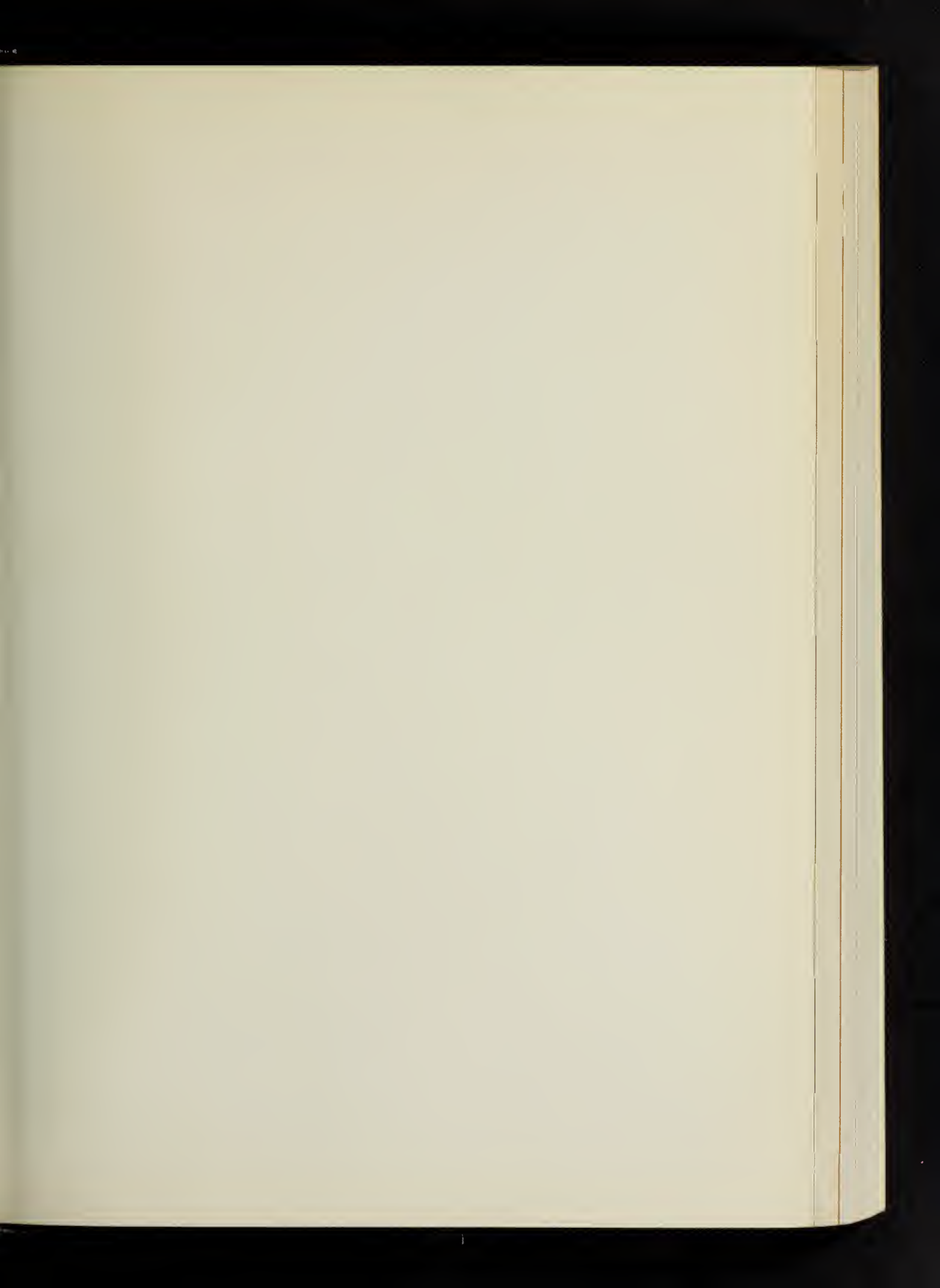
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Public Health Service

PSYCHOPHARMACOLOGY ABSTRACTS is a publication of the National Clearinghouse for Mental Health Information of the National Institute of Mental Health. It is a specialized information medium designed to assist the Institute in meeting its obligation to foster and support laboratory and clinical research into the nature and causes of mental disorders and methods of treatment and prevention. Specifically, this information service is designed to meet the needs of investigators in the field of psychopharmacology for rapid and comprehensive information about new developments and research results.

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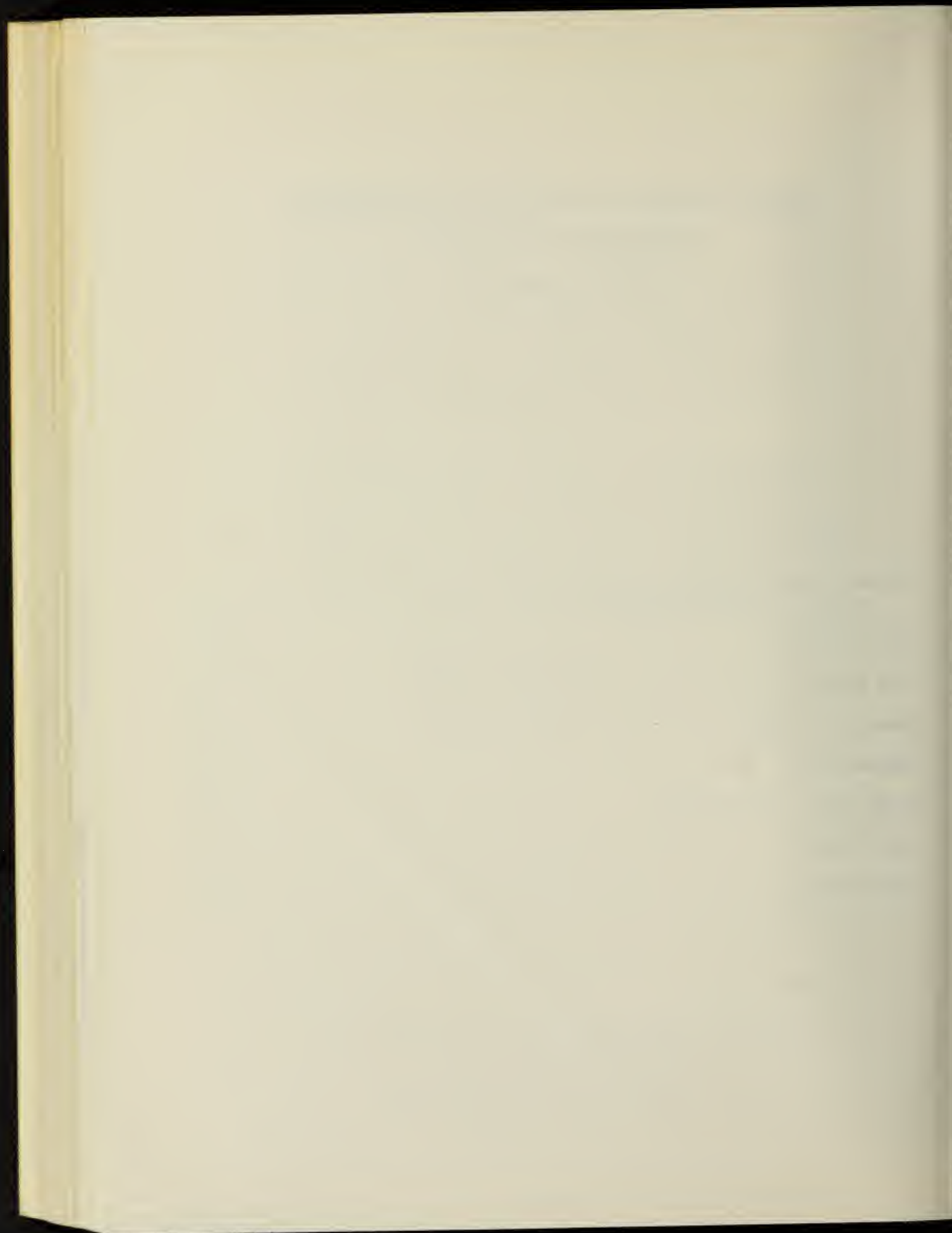
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REVIEWS, SUMMARIES, BIBLIOGRAPHIES, GENERAL ARTICLES AND BOOKS

- 2406 Charalampous, K. D., ed. **The long-term care of the chronic mentally ill patient, a medical approach.** Medical Record and Annals, 56:257-258, 1963.

The aftercare of the chronic mentally ill patient was discussed, and the results of two studies of patients kept on ataractic drugs after their discharge were given. In the first study, 173 schizophrenic outpatients, followed for 18 months, were given either a phenothiazine tranquilizer or a placebo. In the promazine group (55 patients) 18.2% were rehospitalized; in the chlorpromazine group (62 patients) 4.8% were rehospitalized; and in the placebo group (56 patients) 28.6% were rehospitalized. In the second study, 600 patients, followed for 4 to 10 months, were maintained on drugs or placebo. In the placebo group, 35.1% were rehospitalized and 14.6% in the aftercare group were rehospitalized. Those who were readmitted and who had received aftercare stayed for about 10 days, whereas those who were readmitted and who had received no aftercare remained for about 36 days. An aftercare clinic, which had been in existence for 10 months and had followed 500 patients on drugs, showed an attrition rate of 10% within 6 months as compared with a 50% rate in most clinics. It was concluded that many chronic mental patients can be maintained in the community if properly kept on ataractic drugs.

Baylor University College of Medicine
Houston, Texas

- 2407 Sutherland, James M. **Observations on relationships between drug therapy and neonatal jaundice.** Annals of the New York Academy of Sciences, 111:461-471, 1963.

Meaningful relationships between drugs and neonatal jaundice have resulted from several types of study and comparison. Several of these studies are briefly discussed. Vitamin K has been found to increase the serum bilirubin levels in infants whose mothers had received 72 mg of menadione sodium bisulfite prior to delivery. The serum bilirubin was higher

in infants receiving vitamin K over a 3-day period (10 mg daily) than in those receiving a single 1-mg injection, as measured on the fifth day. The serum bilirubin was lower in infants whose mothers had received meperidine, but not significantly so. There does not appear to be a significant relationship between phenothiazine drugs administered to mothers and neonatal icterus. A highly significant number of infants, whose mothers had received 72 mg of vitamin K, required replacement transfusion. The infants of sulfisoxazole-treated mothers had lower serum bilirubin than did the controls. Novobiocin (cathomycin) (150 mg/day) produced a threefold increase in the serum bilirubin. A decrease in neonatal hyperbilirubinemia was observed in infants receiving 150 mg/day of erythromycin p.o. for staphylococcal infection.

University of Cincinnati
Cincinnati General Hospital
Children's Hospital Research Foundation
Cincinnati, Ohio

- 2408 Andresen, Albert F. R., Jr. **A practical approach to anxiety reactions.** New York State Journal of Medicine, 63:1144-1147, 1963.

Anxiety reactions are discussed, and a simple method of dealing with the problem of psychotherapy in medical practice is presented. Symptoms of autonomic stress may be neurologic, cardiac, pulmonary, gastrointestinal, or dermatologic. In the therapy of anxiety reactions, an attempt must be made to determine the conflicts that have produced tension and to propose adequate outlets for these tensions, as well as to control the symptoms that may have developed as a result of organic reaction to autonomic stimulation.

421 Huguenot Street
New Rochelle, New York

REVIEWS 2409-2412

- 2409 Keeler, Martin H. **The use of hallucinogenic, psychotomimetic, psychedelic drugs in North Carolina.** North Carolina Medical Journal, 24:555-557, 1963.

The pharmacology of the hallucinogenic, psychotomimetic, or psychedelic reaction is essentially unknown. Comparison of these drug effects is made with various symptoms present in various psychiatric illnesses. The use of these drugs by psychiatrists is to assist in the uncovering of emotions or memories and in the therapeutic value of the psychedelic or mind-releasing action. The drugs are not addictive, but may be habituating. The illegal use of these drugs may become a minor problem in student populations.

Department of Psychiatry
University of North Carolina
School of Medicine
Chapel Hill, North Carolina

- 2410 Lehmann, H. E. **Use and abuse of phenothiazines.** Applied Therapeutics, 5:1057-1069, 1963.

The tranquilizing effect of the phenothiazines is due to a selective inhibition rather than to a global inhibitory action on the CNS as seen with many of the older drugs. The most distinctive pharmacological property of all phenothiazines is their neuroleptic action. Most of these drugs have an antipsychotic action, and are characterized by a wide spectrum of therapeutic activity and also a large array of side effects, which, for the most part, are not serious. They may be used in the treatment of psychiatric illness or for nonpsychiatric indications. Chlorpromazine may be used in daily doses of 25 mg to 5,000 mg daily for symptomatic treatment. Some of the side effects are orthostatic hypotension, syncope, photosensitivity, and extrapyramidal symptoms. Agranulocytosis and jaundice are rare side reactions. Phenothiazines are used in long-term maintenance therapy and in the treatment of the chronic psychotic. A discussion is presented of the use of major and minor tranquilizers.

Verdun Protestant Hospital
McGill University
Montreal, Canada

- 2411 Killam, Keith F. **Chapter 12. Why certain substances correct neural abnormality.** Progress in Neurobiology, 5:378-390, 1962.

The present state of the knowledge of how drugs may act on the nervous system, and the approaches that are available, together with their limitations, are presented. Little or nothing is known about the exact mechanisms by which drugs correct neural abnormality. In considering the possible approaches to the study of drug effects on neuronal activity, there appear to be five levels of investigation: drug action on biochemical processes, on the responses of single cells, on cell populations and integrative systems, on the relation of basic behavior patterns to electrical activity of the brain, and the actions of chemical compounds on the acquisition and performance of complex behavior patterns and the correlated activity of neurons in the brain. The correlation of each of the levels of study with the basic function of the CNS (generation of behavior) is of major importance in the study of drug effects.

(No address)

- 2412 Jenkins, Sidney B. **The use and abuse of phenothiazines in treatment of acute psychoses.** Journal of the National Medical Association, 55(6):515-519, 1963.

The phenothiazines tend to affect both the general and specific psychotic symptoms. The drugs should be used mainly for treating patients who have experienced psychotic episodes. Adequate dosage and the prolongation of the treatment period, if necessary, are important factors in treating the mentally ill. These drugs tend to reverse the psychopathology. The clinical effects of 10 phenothiazines are presented. These drugs are not interchangeable, and selection should be based on the symptoms to be treated. The use of phenothiazines with barbiturates and antidepressants should be avoided. The patient must be carefully followed up after discharge.

Wayne County General Hospital
Eloise, Michigan

- 2413 Lesse, Stanley. **Psychodynamic consideration in current psychopharmacologic practices.** *Psychosomatics*, 4:353-358, 1963.

A discussion is presented of the psychodynamic mechanisms that transpire when clinical changes occur as the result of administration of psychotropic drugs. Tranquilizing drugs are effective, with rare exceptions, only with patients who overtly manifest a moderate to marked degree of anxiety. The greater the quantitative degree of anxiety, the more dramatic the therapeutic results. Four basic components of anxiety are motor (tension), affective, autonomic, and verbal. Amelioration of anxiety proceeds in a systematic fashion according to these four components. Decrease in the motor component is the first sign of anxiety decompression. The use of ataractic drugs with psychotherapy permitted the establishment of a strong positive transference in a matter of weeks. In evaluating improvement of severely depressed patients following administration of antidepressant drugs, psychomotor activity improvement preceded any improvement in the depressed affect. A more intense transference relationship was developed when antidepressant drugs and psychotherapy combined were used than when psychotherapy alone was used. The pretreatment level of various intrapsychic functions determines, in large part, the results that will be obtained by any type of therapy. Chlorpromazine is a function-inhibiting agent that has the greatest effect when the initial value of anxiety is high.

Neurological Institute
Presbyterian Hospital of New York
New York, New York

- 2414 Lehmann, H. E. **Psychopharmacology. A discussion of current problems.** *Ohio State Medical Journal*, 59:1091-1097, 1963.

A general discussion is presented of the classification, experimental and clinical trials, therapeutic effectiveness, and side reactions of psychotropic drugs. Classification according to arousal, affect, and integration parameters can provide a more clearly defined system for indicating psychotropic drug effects. Assessment of drugs by controlled and uncontrolled clinical trials is discussed. Difficulty occurs in the extrapolation of data from animal experiments to therapeutic application in human subjects. Chemical,

endocrinological, physiological, physicochemical, and psychological models of drug action are discussed. Psychotropic drugs have been beneficial in treating depression, neuroses, and psychotic anxiety. The therapeutic application of psychotomimetic drugs must, at this time, be considered an experimental procedure.

Verdun Protestant Hospital
Verdun, Quebec, Canada

- 2415 Tan, E. S. **Some aspects of advances in psychiatry.** *Medical Journal of Malaya*, 18(1):30-37, 1963.

Historical development of psychiatry from the late 1800's to the present is presented. Included are the use of drugs, ECT, and insulin shock therapy. Chlorpromazine was the first of a series of psychotropic drugs introduced. Psychotropic drugs are divided into two groups—tranquilizers or neuroleptics and antidepressants or thymoleptics. These two groups of drugs and ECT form the main props, as it were, of physical treatment in psychiatry today. The chemical structure and activity of representative drugs from these groups are discussed. Iproniazid was the first drug in the series of antidepressants. Modified bimodal leucotomy is useful for the chronic obsessional neurotic with a good premorbid personality and does not produce marked personality changes, but relieves the psychiatric symptoms. Freudian theory of psychoanalysis is discussed. The use of individual psychotherapy, group therapy, and behavior therapy is described. Psychological tests provide psychiatrists with more objective and valid measures of mental function.

Tampoi Mental Hospital
Johore Bahru, Malaya

- 2416 Pare, C. M. B. **Diagnosis and management of depression.** *Current Medicine and Drugs*, 3:26-46, 1963.

Endogenous depressions are characterized by change of mood. Positive and negative symptoms of affective illness are outlined. Predisposition to a depressive illness is inherited. A faulty diagnosis of neurosis instead of depressive illness is common when the depression is mild. In the more severe depressive illnesses, the positive symptoms predominate and diagnosis is rarely in doubt. Various manifestations of a depressive illnesses are discussed. For proper management, an assessment of the etiological factors

is important. Illustrations are presented for each diagnostic type---chronic, neurotic, reactive depressive, the endogenous depressive, and depression secondary to organic illness. The treatment plan is formulated along three lines: removal of stressor factors, assisting the patient to better adjust by means of psychotherapy, and physical treatment. Suicide is the biggest hazard of depressed patients, and the physician must assess this risk. Treatment includes drug therapy, psychotherapy, the use of local social facilities, and ECT. Monoamine oxidase inhibitors are useful in the treatment of depression, as is the imipramine group of drugs. Side reactions are given for these drug groups. A discussion is presented of the indications for combined ECT and antidepressant therapy.

(No address)

- 2417 **Brain amines.** South African Medical Journal, 37:746, 1963.

The roles of brain amines, noradrenaline, and 5HT are discussed. Various drugs have been studied with relation to their effects on these amines.

(No address)

- 2418 de Ajuriaguerra, J., ed. **Monoamines et système nerveux central.** (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Geneva, Georg, 1962. 277 p.

A list is given of the titles of reports presented at a symposium of clinicians, neurophysiologists, and biochemists held in September 1961 at the Psychiatric Clinic of the University of Geneva (Bel-Air). Topics presented include studies on serotonin, DOPA analogs, brain monoamines, monoamine oxidase, drug-induced alterations in the metabolism of cerebral monoamines, monoamines and behavior, MAO inhibitors in the treatment of mental disorders, and the role of catecholamines in parkinsonism.

Georg and Company S.A.
Geneva, Switzerland

- 2419 Brodie, Bernard B. & Costa, E.

Some current views on brain monoamines. In: de Ajuriaguerra, J., ed. **Monoamines et système nerveux central.** (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 13-49.

Processes that comprise the amine storage unit, such as synthesis, storage mechanisms, release and metabolism, and drugs that affect amine reactive sites, either directly or indirectly, by blocking these processes are discussed.

National Heart Institute
National Institutes of Health
Bethesda, Maryland

- 2420 Zeller, E. Albert. **Monoamine oxidase.** In: de Ajuriaguerra, J., ed. **Monoamines et système nerveux central.** (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 51-57.

The distribution of MAO, its multiple nature and its biological role are discussed. Monoamine oxidase is present in the cells of all three germ layers---ectodermal, mesoderm and endodermal. The activity of MAO varies between species, organs, sex, age, and the kind of cell. Quantitative and qualitative differences exist between monoamine oxidases of various origin. The evidence indicates that MAO plays a role in the metabolism of catecholamines and other amines.

Department of Biochemistry
Northwestern University Medical School
Chicago, Illinois

- 2421 Gottfries, C. G. **Clinical assessment of the value of monoamine oxidase inhibitors in the treatment of mental disorders.** In: de Ajuriaguerra, J., ed. **Monoamines et système nerveux central.** (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 209-214.

Various MAO inhibitors have been used mainly in the treatment of depressive states and neuroses of different types. Iproniazid has been used in the treatment of more serious depressive states. It is assumed that the MAO inhibitors have the same mode of action, the most striking effect being one of stimulation. Improvement

in the feeling of well-being is another psychic effect. The effects of MAO inhibitors are less strong and more prolonged than those of amphetamine. A comparison is made of the therapeutic effects and side reactions of iproniazid (75 to 150 mg/day), Ro 4-1038 (10 to 60 mg/day), pheniprazine (24 mg for 3 days, 12 mg/day), and nialamide (75 to 300 mg/day). Nialamide and possibly pheniprazine had not only a less marked therapeutic effect but also produced less side reactions. A reduction in the urinary excretion of mandelic acid was also noted.

General Hospital of Malmö
Department of Psychiatry
Malmö, Sweden

- 2422 Kielholz, P. & Labhardt, F.
Dédutions tirées de nos connaissances sur les inhibiteurs de MAO par rapport à la classification classique des psychoses. (Deductions relative to the classical classification of psychoses based on knowledge of the MAO inhibitors.) In: de Ajuriaguerra, J., ed. Monoamines et système nerveux central. (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 233-238.

On the basis of the present knowledge concerning the treatment of psychiatric illnesses with MAO inhibitors, several conclusions have been reached. In the depressive illnesses, favorable therapeutic effect has been obtained with MAO inhibitors in all diseases in which symptoms of inhibition, lack of initiative, and fatigue dominate. This activation of previously latent manic forms reveals the endogenic nature of depression, enabling differential diagnosis. Differential nosological diagnosis is also possible in depression on a background of schizophrenia, by heightening latent schizophrenic traits, different from psychoses due to MAO inhibitor intoxication. Various observations (latent period preceeding manifestation of effect, weak antidepressive action of weak MAO inhibitors, antidepressive action of MAO inhibitors with the exception of hydrazine) enable the conclusion that a direct correlation probably exists between the antidepressive action of MAO inhibitors and inhibition of MAO. No observations thus far enable a conclusion concerning the role played by the inhibition of MAO in psychoses. Since both the typical antidepressive effect and the effect of the above latent traits are observed with drugs that do not act on MAO,

the mechanism of inhibition of MAO cannot definitely be cited as responsible for the psychotic phenomena mentioned.

Psychiatric Clinic
University of Basel
Basel, Switzerland

- 2423 Cazzullo, C. L., De Martis, D., & Terranova, R. Retentissement des connaissances expérimentales des monoamines sur les classifications nosographiques classiques. (Application of experimental data on monoamines to the classic nosographic classifications.) In: de Ajuriaguerra, J., ed. Monoamines et système nerveux central. (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 239-246.

The MAO inhibitors (MAOI) have been discussed in terms of their diagnostic use in revealing the depressive symptom in complex syndromes. Side effects of MAOI's were discussed in general terms, based on their effects on the nervous system (EEG) and extraneous organs (liver, etc.). Experimental observations show that there is a correlation between pharmacological and clinical observations in regard to excitation and to action on psychomotor activity. Correlation between the action of MAOI's and MAO inhibiting action and antidepressive action is less equivocal. Pheniprazine, for example, has high MAO inhibiting action, but is no more effective than isocarboxazid or tranylcypromine in antidepressant efficacy. The MAOI treatment has a remarkable diagnostic use in revealing the depressive symptom in complex syndromes. It was concluded that the nosographic aspect of mental illness must still be related to the classic concepts until experimental biological data are able to furnish the statistically valid basis for more precise classification.

Psychiatric Clinic
University of Milan
Milan, Italy

2424 Deniker, Pierre. Monoamines, médicaments psychotropes et nosographie psychiatrique. (Monoamines, psychotropic drugs, and psychiatric nosography.) In: de Ajuriaguerra, J., ed. Monoamines et système nerveux central. (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 215-232.

This paper discusses: (1) the classification of psychotropic drugs in relation to monoamines; (2) the effects of psychotropic drugs according to nosographic groups; and (3) the neurological, or side effects, of psychotropic drugs. Data show psycholeptic drugs (sedatives) have an antiadrenergic action with monoamines; on the other hand, psychoanaleptic (stimulants) and psychedelic drugs (pathogens) have an adrenergic action with monoamines. In reviewing studies on nosographic groups, it is shown that hyperactive, psychopathic states (manic depression, acute schizophrenia) are accompanied by an increased catecholamine excretion, and deficiency states (senile dementia, mental retardation) are accompanied by the diminution of catecholamine excretion. Thus, preferred therapeutic drug treatment for manic depressives should be imipramine and MAO inhibitors; for acute schizophrenia, the phenothiazines and reserpines are indicated; and the stimulants, such as amphetamines, are preferred for senile dementia. The side effects produced by the psycholeptics, in particular, the neuroleptics (phenothiazines, reserpines, and butyrophenones), are extrapyramidal syndrome, dyskinesia, and vegetative disorders; with the psychoanaleptic drugs, the antidepressants (imipramine, MAO inhibitors, and amphetamines), convulsions are the side effects produced.

Clinic of Mental and Brain Disorders
Paris Faculty of Medicine
Paris, France

2425 Achelis, J. D. & Ditfurth, H., eds. Anthropologische und naturwissenschaftliche Grundlagen der Pharmako-Psychiatrie. Starnberger Gespräche, 1961. (Anthropological and scientific bases of psychopharmacology. Starnberg Conference, 1961.) Stuttgart, Georg Thieme Verlag, 1963. 113 p.

This conference reviews the current status of psychiatry in Germany in the light of anthropological psychiatry and behavioral pharmacology. The various papers examine drive, affectivity, aggression, and anxiety

in the animal, as well as their changes. In this respect, the organs in relation to expression of affect, have an entirely new functional interrelationship that cannot be covered by classical pharmacology. In the present conference, behavior is considered as having exogenous drive. Because no model psychoses are available for study by means of the pharmacology of behavior, higher functions of the nervous system are tested, and the results are evaluated as to whether or not they conform to psychoses. It is shown that behavioral phenomena belong to the physiology of the nervous system to the same extent as the reflexes and regulatory processes.

Mannheim, Germany

2426 Straus, E. Die Verwechslung von Reiz und Objekt. Ihr Grund und ihre Folgen. (The exchange between stimulus and object. Its basis and consequences.) In: Achelis, J. D. & Ditfurth, H., eds. Anthropologische und naturwissenschaftliche Grundlagen der Pharmako-Psychiatrie. Starnberger Gespräche, 1961. (Anthropological and scientific bases of psychopharmacology. Starnberg Conference, 1961.) Stuttgart, Georg Thieme Verlag, 1963, p. 4-32.

In relation to its methodology, behavioral psychology excludes all introspection and limits itself to objective experiences, observations, and meanings. However, the prevailing opinion that all behavior may, in the last resort, be reduced to events within the organism takes too much for granted. For example, in a discussion of the behavior of a turkey hen during the silence between successive tone stimuli, it is suggested that the stimuli actually comprise a continuum of successive tones and silences. The stimulus-reaction pattern is a problem peculiar to the theory of perception. However, although the observer and the observed are part of the same experimental field, they are not interchangeable, and the observer must distinguish between cause and effect. The history of the relationship between stimulus and object in the physiological sense is reviewed, beginning with the 16th Century.

(No address)

2427 Zutt, J. *Der Leib der Tiere.*

(*Möglichkeiten und Grenzen pharmakologischer Einwirkungen auf das Verhalten*). (The body of the animal. (Possibilities and limitations of pharmacological effect on behavior).) In: Achelis, J. D. & Ditfurth, H., eds. *Anthropologische und naturwissenschaftliche Grundlagen der Pharmako-Psychiatrie. Starnberger Gespräche*, 1961. (Anthropological and scientific bases of psychopharmacology. Starnberg Conference, 1961.) Stuttgart, Georg Thieme Verlag, 1963, p. 33-52.

Following philosophical observations concerning the human body, the author discusses that which may be applied from what we know of the human body to the animal body, and the essence and the limits of pharmacological effects on man and animals. Animals lack the psychic dimension and are only "body." They possess behavior without learning and without experience, which is essentially equivalent to instinct. However, involvement of the animal body in a situation comprises a true movement of the animal, not merely muscular contraction, retraction, or extension of an extremity, nor one of the many isolatable functions of the animal body. In all situations in which the body is involved, the internal medium is the determining and modifying one. The biochemical circumstances of the body, including pharmacological action, comprise the material facilitating and mediating basis of the body.

Frankfurt-am-Main, Germany

2428 Selbach, Helmut. *Über regulationsdynamische Wirkgrundlagen der Psychopharmaka.* (The dynamic regulatory bases of action of psychopharmacological agents.) In: Achelis, J. D. & Ditfurth, H., eds. *Anthropologische und naturwissenschaftliche Grundlagen der Pharmako-Psychiatrie. Starnberger Gespräche*, 1961. (Anthropological and scientific bases of psychopharmacology. Starnberg Conference, 1961.) Stuttgart, Georg Thieme Verlag, 1963, p. 53-74.

The most often used psychopharmacological agents may be divided into two groups on the basis of principles of action—neuroleptics and thymoanaleptics. The overall concept of neuroleptic action may be closely equated to the terms cholinergic, parasympathicotropic, sympathicolytic, and adrenolytic. In simplified form, the action of thymoanaleptics may be identified with the terms adrenergic, sympathicotropic, parasympathicolytic, and cholinolytic. A fact of basic importance is that compounds of both these large effect groups act on

both of the vegetative partial systems, and thus have central, antiadrenergic, and anticholinergic effect, but with different degrees of intensity. In the action of both the phenothiazines and imipramines, differentiation must be made between an initial, or turbulent, phase and the cure phase, each of which has subphases. In addition to multiphase effect, these psychopharmacological agents have a vegetative difference effect, with simultaneous antiadrenergic and anticholinergic effect on vegetative control centers, but with different intensities. Explanations are offered for the concomitant phenomena of thymoanaleptics and their effect on the therapeutic outcome. A scale of efficacy is given for psycholeptics and psychoanaleptics, based on the motor and vegetative systems and on the psyche.

Berlin, Germany

2429 Von Baeyer, W. *Zur klinischen Erprobung der Psychopharmaka.* (On the clinical testing of psychopharmacological agents.) In: Achelis, J. D. & Ditfurth, H., eds. *Anthropologische und naturwissenschaftliche Grundlagen der Pharmako-Psychiatrie. Starnberger Gespräche*, 1961. (Anthropological and scientific bases of psychopharmacology. Starnberg Conference, 1961.) Stuttgart, Georg Thieme Verlag, 1963, p. 100-112.

In the clinical evaluation of psychopharmacological agents, the first step is the clinical impression. The following step, through clinical case analysis, too often is omitted in hurrying on to measurement of affects. The clinical pharmacological "input" may be readily measured, and the psychopathological phenomena may be measured in terms of duration of a psychosis or psychotic phase, degree of remission, and symptoms. The unclear zone of psychophysical processes between pharmacological input and psychopathological phenomena can be brought to light by the clinician through the rough cross section of causal relationships that may be established through the above. Several psychopharmacological fundamental experiences must be taken into account, especially in statistical processing of drug evaluation. These include three pairs of concepts: proper effect and clinical effect of a drug; drug-bound and drug-outlasting effect; and overall sedation and a specifically organizing effect.

Heidelberg, Germany

REVIEWS 2430-2434

2430 Ministry of Health, U.S.S.R.

Aktual'nyye voprosy psikhii i nevropatologii. (Current problems of psychiatry and neuropathology.) Morozova, G. V., ed. Moscow, 1963. 559 p.

Studies based on the pathophysiological mechanisms and pathogenesis of several psychiatric diseases are discussed, and literature dealing with the diagnosis and treatment of a variety of mental illnesses is presented. Neuropsychiatric disorders and electrophysiological studies are also included. Pharmacological agents used in the treatment of mental illness were antidepressants, MAO inhibitors, barbiturates, and hallucinogens.

Ministry of Health
Moscow, U.S.S.R.

2431 Khaletskiy, A. M. **On the problems and possibilities of pharmacodynamic investigation of the mentally ill.** In: Ministry of Health, U.S.S.R. **Aktual'nyye voprosy psikhii i nevropatologii.** (Current problems of psychiatry and neuropathology.) Morozova, G. V., ed. Moscow, 1963, p. 58-67.

A discussion of the pharmacological activities of several preparations in the treatment of mental illnesses is presented. The main significance of pharmacodynamic research is in the possibility of sometimes intensifying and eliminating hidden, latent symptoms of the mental defect, which is behind the psychopathological superstructure. The use of hexenal is recommended for this purpose. The diagnostic application of experimental narcosis is suitable for patients who are inaccessible to contact or who dissimulate their hallucinatory-delirious emotions. However, narcopsychotherapy or narcoanalysis must be rejected.

Astrakhan, U.S.S.R.

2432 Ditman, Keith S. **Psychotomimetics: Pharmacodynamic and psychotherapeutic properties.** Proceedings of the Western Pharmacology Society, 6:13-17, 1963.

The behavioral effects of the psychotomimetics cannot be explained; however, the psychopharmacological effects on 74 LSD subjects are presented. Similarities in the responses to LSD, placebo, and religious conversions are presented. Consideration is given to the view that, although the psychotomimetics have potent effects, they may act mainly as

"super placebos." The psychotomimetics are potentially powerful persuaders due to the intense euphoria and sense of profundity they produce.

Department of Psychiatry
UCLA Medical Center
Los Angeles, California

2433 Hollister, Leo E. **Newer developments in the clinical study of psychotherapeutic drugs.** Proceedings of the Western Pharmacology Society, 6:61-63, 1963.

The present techniques involved in the clinical study of antipsychotics and antidepressants are discussed. Since the superiority of the antipsychotic drugs has been proven, they no longer need placebo or ineffective drug controls. Two "standard" drugs used in blind controlled studies are acetophenazine and perphenazine. The technique used for antidepressant drugs involves the use of concurrent placebo controls, and thus far, imipramine and amitriptyline may be considered as effective, but the hydrazines are too unpredictable. The present technique for evaluating drug combinations is adequate, but no satisfactory technique has been found for evaluating the therapeutic potential of psychotomimetic drugs.

Veterans Administration Hospital
Palo Alto, California

2434 Kissen, Martin D. **The management of acute withdrawal symptoms of alcoholism.** Journal of the American College of Neuropsychiatry, 1:9-13, 1962.

The role of the general practitioner in dealing with the alcoholic, as well as the mechanics of the treatment of acute and chronic alcoholism are discussed. The therapy of acute alcoholism is primarily physiologic, whereas that of chronic alcoholism is psychiatrically oriented. Chlordiazepoxide, when studied in 80 patients admitted to the clinic and in 67 outpatients with postalcoholic anxiety reactions, was found to be very effective in both the management of acute alcoholism and of the anxiety reaction in the sober alcoholic. In acute alcoholism, the drug was given at a dose of 100 mg at bedtime i.v., i.m., or p.o. on the admission day and 10 mg q.i.d. orally for the remainder of the hospital

stay. In anxiety reactions, the drug was given in dosages from 10 mg b.i.d. to 25 mg q.i.d.

St. Luke's & Children's Medical Center
Philadelphia, Pennsylvania

2435 Schultz, John D. **The treatment of psychiatric patients in a general hospital and the newer psychopharmaceutical agents.** *Journal of the American College of Neuropsychiatry*, 1:36-44, 1962.

Factors influencing the trend of successful management of psychiatric patients, other than the use of psychotropic drugs, in general hospitals are: (1) the recognition of the functional aspects of somatic disease; and (2) the need for training programs and for association among the doctors and their colleagues. The physical organization, treatment of patients, types of patients admitted, and the staff (professional and nonprofessional) of a large general hospital are discussed. Maximum freedom to communicate and the resolution of interpersonal barriers among the staff is most important for the establishment of a receptive milieu. The accommodations should more closely resemble those of a modern hotel, with emphasis on simplicity, functional efficiency, comfort and tasteful decor. The physical medical rehabilitation program, including occupational therapy, is an important facet of the treatment regime. Psychotropic drugs have been classified into two groups---those that seem to facilitate the integration of autonomic, somatic, and psychic function and are excitatory, and the trophotropic drugs that produce a state of apathy. The selection of the drug must relate to the functional situation. Alcoholics have been successfully treated with chlordiazepoxide. Drug addicts were treated with promazine to alleviate the stress of the withdrawal syndrome.

D.C. General Hospital
Washington, D.C.

2436 U.S. Public Health Service. **Behavioral research in preclinical psychopharmacology. Issues of design and techniques.** (National Institutes of Health.) Washington, Superintendent of Documents, U.S. Government Printing Office, 1962, 23 p.

In this document an attempt is made to state clearly some of the prime considerations of research studies in psychopharmacology as

follows: (1) Clarify what procedures were used. (2) Aid the investigator in specifying those conditions under which he plans to carry out his study. (3) Specifically identify those important variables that are studied and those variables that are fixed, uncontrolled, or ignored.

Psychopharmacology Service Center
National Institutes of Health
Bethesda, Maryland

2437 McAtee, Ott B. **Tranquilizing drugs, alcohol, and the physician's responsibility.** *Journal of the Indiana State Medical Association*, 56:1008-1011, 1963.

Some of the dangers and hazards in the use of tranquilizing drugs are discussed. It has been found that when meprobamate and chlorpromazine are taken with alcohol, performance and judgement are impaired, and depth perception and coordination are affected. Patients should be warned not to drink while taking these drugs; this caution probably should apply to all tranquilizers.

Madison State Hospital
Madison, Indiana

2438 Lieberman, Arnold. **The case of the barbed barbiturate.** *Journal of the Indiana State Medical Association*, 56:1426-1431, 1963.

Two cases of barbiturate poisoning are discussed. In both cases, the main point, barbiturate abuse, was emphasized. A woman was told to take one phenobarbital tablet (100 mg) after dinner and one tablet before bedtime for nervousness. Two weeks later, the patient was found in a confused condition after taking "an extra one or two" tablets. Later in the day, the patient ingested 22 pills within one-half hour, and after recovery, she could not recall taking the pills. It was concluded that automatism had occurred. In the second case, a woman was found in a coma after taking about 12 tablets of an aspirin compound. Upon analysis of the blood and urine, barbiturate was found in lethal amounts. She recovered, but some time later, died due to an overdose of seconal.

1270 Fifth Avenue
New York, New York

REVIEWS 2439-2443

- 2439** Turnbull, T. A. **Man-induced hyperpyrexia.** *Journal of the Royal Naval Medical Service*, 49:169-175, 1963.

In a review of the literature of drug-induced hyperpyrexia, the results of several clinical trials of drugs are cited. Most cases of drug-induced heatstroke reported are associated with belladonna or similar synthetic alkaloids, and occasionally with antihistamine, antispasmodic, or tranquilizing drugs. It is concluded that the prescribing of drugs with anticholinergic properties may be the final factor in precipitating heatstroke.

(No address)

- 2440** Stevens, Harold. **The management of parkinsonism.** *Maryland State Medical Journal*, 12:494-497, 1963.

The objectives and targets of therapy of parkinsonism are listed, and the therapeutic measures that may be used are discussed. Physical therapy should be initiated as soon as the diagnosis is made. Drug therapy is based mainly on the synthetic parasympatholytic drugs that should first be given at the minimum effective dosage and then increased in dosage. Surgery at the present time is limited to 10% to 20% of Parkinson patients, but it is receiving wider application. Psychotherapy has a supportive effect and is a most important element in the management of patients with parkinsonism.

George Washington University
School of Medicine
Washington, D.C.

- 2441** Baker, A. A. **Treating schizophrenic mothers with their babies.** *Children*, 10(3):114-115, 1963.

This report discusses the work being carried out at Banstead Mental Hospital, Surrey, England, which has a mother and baby unit for the care of schizophrenic mothers admitted with their babies. It was shown that 100% of the mothers admitted with their babies left the hospital able to care for their babies as compared with 60% of the mothers who were not accompanied by their babies. The case of a Belgian immigrant admitted to the hospital after showing paranoid schizophrenic tendencies following childbirth is cited. She responded to electroconvulsive therapy in

combination with a tranquilizer, and was discharged after 10 weeks. It is concluded that this type of unit not only provides therapeutic advantage to the patient, but to the family and community as well.

Banstead Mental Hospital
Sutton, Surrey, England

- 2442** Bell, Richard Q. **Some factors to be controlled in studies of the behavior of newborns.** *Biologia Neonatorum*, 5:200-214, 1963.

This paper summarizes studies indicating the methodological importance to neonatal behavior of a number of factors including: (1) the level of arousal or state of the infant; (2) effects of being first born; (3) complications of pregnancy and delivery; (4) effects of analgesics and anesthetics; (5) effects of bottle-feeding versus breast feeding and interaction effects with number 4; (6) age differences and their interaction with numbers 3 and 4. It is suggested that suitable experimental and statistical controls be provided until relationships are worked out between various behaviors of the neonate and the special circumstances existing in the early period. One type of research design is suggested, which might be appropriate for many studies, and which would make allowances for the effect on the results of the various behaviors and special circumstances.

Section on Infant Development
National Institutes of Health
Bethesda, Maryland

- 2443** Shepherd, Michael & Wing, Lorna. **Pharmacological aspects of psychiatry.** In: Garattini, Silvio & Shore, Parkhurst A., eds. *Volume I. Advances in pharmacology.* New York, Academic Press, 1962, p. 227-276.

Several important aspects of pharmacology are examined. The functioning of the adrenergic nerve fiber is discussed in detail, and different aspects of the biogenic amines are presented. Some of the newer drugs (antihypertensive drugs, psychotropic drugs, and drugs that control hyperlipidemia) and their possible mechanisms of action are discussed. Pharmacological considerations in antithrombotic therapy

are presented, and the ways in which drugs can increase or decrease the rate of drug metabolism are examined.

Institute of Pharmacology
University of Milan
Milan, Italy

2444 Chancé, Pierre & Chancé-Serve, Claude.
**Memento de thérapeutique neuro-
psychiatrique.** (Memoranda of neuropsychi-
atric therapy.) Paris, Masson, 1963. 253 p.

This notebook of neuropsychiatric therapy is based on the professional experience of two neuropsychiatrists. The book is intended mainly as an aid to the general practitioner who occasionally finds it necessary to treat a neurosis or psychosis on an outpatient basis, but it is applicable also to specialists of all areas. It deals with the prescription of neuroleptics, tranquilizers, antidepressants, and antiepileptic and antiparkinsonian agents, including classification of the drugs, pharmacodynamic, clinical and psychophysiological properties, indications, daily doses, equivalent doses, and commercially available forms.

Libraries of the Academy of Medicine
120 Boulevard Saint-Germain
Paris, France

2445 Jundzill, Krystyna. **Polskie
piśmiennictwo neurologiczne,
neurochirurgiczne i psychiatryczne za rok
1962.** (Polish literature on neurology,
neurosurgery and psychiatry published in
1962.) *Neurologia Neurochirurgia i
Psychiatria Polska*, 13:731-753, 1963.

A list of all the 1962 Polish publications in the fields of neurology and psychiatry is presented. The topics covered under the neurological field are neuropathology, neurophysiology, diagnosis, symptomology, treatment, neuropharmacology, and neurosurgery. Topics covered in the psychiatric field are history, pathogenesis, symptomology, diagnosis, and therapy.

(No address)

CLINICAL STUDIES

- 2446 Brown, David. **Antepartum haemorrhage and placenta praevia.** Medical World, 99:108-110, 1963.

The management of antepartum hemorrhage (APH) in the home and in the hospital (before or after 38 weeks' gestation) is discussed. All cases of APH are treated in hospital as placenta praevia, unless proven otherwise. Placenta praevia should be thought of when the fetal head or breech is still floating freely about the pelvic brim within the last few weeks of pregnancy. Digital vaginal or rectal examinations may be performed only in operating theaters where preparations have been made for a Caesarean section. An i.v. injection of a tranquilizer, such as 50 mg promazine HCl, may be given for shock and restlessness.

St. John's Hospital
Chelmsford, Essex, England

- 2447 Mulla, Nejdat P. **Management of the menopausal patient with amitriptyline.** American Journal of Obstetrics and Gynecology, 87(1):137-138, 1963.

This investigation was made in order to find a form of therapy that would provide adequate results in menopausal patients and obviate the risk of excessive barbiturate administration. Each of 100 patients complaining of symptoms due to either physiological or surgical menopause received amitriptyline (10 mg q.i.d.) for 2 months and then equine estrogen (0.625 mg/day) was added to the test drug for another 2 or 3 months. Sixty-two of the women responded satisfactorily to amitriptyline alone; this response increased to 92 patients with the addition of estrogen. Vasomotor symptoms were not adequately relieved, and those patients having hot flashes required estrogen. No side-effects or adverse reactions were reported.

Kent, Ohio

- 2448 Goldfarb, Arthur A. & Venutolo, Felix. **The use of an antidepressant drug in chronically allergic individuals. A double blind study.** Annals of Allergy, 21(12):667-676, 1963.

A double-blind study was made to determine the psychic and somatic efficacy of imipramine on 100 chronic allergic patients suffering from some emotional or psychogenic disturbances. Most of the patients had asthma or allergic rhinitis. A double-blind comparison was made of imipramine, atropine, and placebo. The patients were given either imipramine 25 mg, atropine sulfate 0.1 mg, or lactose placebo in doses of one capsule t.i.d. Patients who showed a favorable effect from imipramine were maintained on 25 mg t.i.d. The psychic results after 6 weeks showed that 54 patients improved on imipramine alone, but not on placebo or atropine; after 1 year 67 patients were greatly improved, whereas 13 did not improve. The effects of imipramine on allergies after 1 year were: 66 patients improved (50 were over 12 years old); 13 did not improve (7 were over 12 years old; and 1 recovered completely. The drug produced no serious psychic effects or marked toxic reactions. Organic side effects observed were dryness of mouth, excessive perspiration, constipation, dizziness, drowsiness, disorientation, and urinary retention. Imipramine was found to be a generally useful and safe drug for allergic patients with depression and anxiety associated with psychoneurosis or aberrations in personality structure.

Allergic Service
Holy Name Hospital
Teaneck, New Jersey

- 2449 Schwartz, E. D. & Smith, J. J. **The effect of chlordiazepoxide on the female reproductive cycle as tested in infertility patients.** Western Journal of Surgery, Obstetrics and Gynecology, 71:74-76, 1963.

The effect of chlordiazepoxide on the menstrual cycle, ovulation, and the pituitary-ovarian axis was evaluated using a group of

35 infertility patients (20 to 40 years of age). Chlordiazepoxide (10 mg b.i.d. or t.i.d.) was given to each patient from day 5 to day 25 of the menstrual cycle. The total number of cycles studied was 96, which included as many as 6 cycles for some of the patients and only 1 cycle for others. No individual abnormal menstrual period was observed, and dysmenorrhea and premenstrual tension were relieved. Before medication, all patients except one were found to be normally ovulating. At the end of this study, all 35 patients were normally ovulating. No effects were observed on the pituitary-ovarian axis. Six of the patients became pregnant while on medication, and two delivered healthy infants; three were 6 or more months pregnant at the time of this report; and one patient had a spontaneous abortion. It was concluded that chlordiazepoxide had no adverse effect of the female reproductive cycle.

75 South Middle Neck Road
Great Neck, New York

2450 Kirchgraber, D. Klinik der Nebenerscheinungen eines "milden" und doch wirksamen neuroleptischen Mittels (Melleril). (Clinical aspects of the side effects of a mild yet effective neuroleptic ("Melleril").) Schweizer Archiv für Neurologie, Neurochirurgie und Psychiatrie, 91(2):412-445, 1963.

The side effects of thioridazine were studied in 307 patients (212 females, 95 males under 20 to over 80 years of age) given 474 courses of treatment with thioridazine between 1959 and 1961. The diagnoses of the patients included: schizophrenias, 197 patients; manic depressives, 29 patients; mixed psychoses, 10 patients; psychogenic reactive neuroses, 22 patients; chronic organic psychoses, 46 patients; and acute exogenic disorders, 3 patients. The duration of the courses of treatment was from less than 7 days to 3 years, and the highest percentage (49%) had courses of treatment of less than 7 days. The total dosages received were from under 500 mg to over 100,000 mg with the highest percentage (65%) receiving a total dosage of 5,000 to 10,000 mg. The daily dosages ranged from under 50 to 400 mg with the highest percentage (43%) receiving 150 mg/day. The maintenance doses ranged from 25 to 300 mg/day with the highest percentage (45%) receiving 125 mg/day. Side effects were of small importance and mainly autonomic in origin. Extrapyramidal syndromes observed in 37 patients (26 females, 11 males) included

parkinsonism in 12 patients, dyskinesia in 4 patients, and isolated extrapyramidal symptoms in 21 patients. These cases of extrapyramidal side reactions were found mainly in the 31 to 40 age group. Vegetative side effects, appearing in 79 patients, included drowsiness in 37 subjects, dry mouth in 20, difficulty in accommodation in 6, nausea in 2, constipation in 1, collapse in 7, vertigo in 5, and anxiety in 1 patient. These side effects of thioridazine were compared in detail with side effects of other neuroleptics.

Burghölzli Psychiatric Clinic
University of Zurich
Zurich, Switzerland

2451 Boucquey, J. P. & Pierloot, R. Etude de l'action de l'Insidon (G 33040) chez 50 malades ambulants atteints de troubles névrotiques et fonctionnels. (A study of the action of Insidon (G 33040) in 50 outpatients with neurotic and functional disorders.) Acta Neurologica et Psychiatrica Belgica, 63(10): 844-861, 1963.

The action of a new iminostilbene derivative, opipramol, was investigated in 50 patients (23 males and 27 females, average age 35 years) with neurosis diagnosis or somatic complaints of a functional (psychosomatic) nature. All of the patients were tested on 37 target symptoms, and 37 patients were submitted to a Cold Pressor Test, to a Schellong Test (measure of physiological surcharge of the neurovegetative system, or study of blood pressure variations under the influence of an external element, ice water) and to a dermatographic test; all of the tests were given before and 15 days after treatment with opipramol (50 mg/day) on 3 days. Clinically the data were analyzed according to symptoms, syndromes, and overall results. The 37 target symptoms were considered according to improvement, whether marked or slight, and also according to the least, most, and average time required to produce the improvement. The improvement in syndromes was based on the degree of improvement and number of component symptoms improved. The overall results showed very good improvement in 16 patients, with 1 relapse; good improvement in patients, with 2 relapses; slight improvement in 12 with 2 relapses; no change in 14 patients; and aggravations in 2 patients. The side effects were of minor importance and of short duration except in the two patients in which the drug was withdrawn due to aggravations. The results

CLINICAL STUDIES 2452-2454

of the Cold Pressor Test showed a correlation between clinical diagnosis and the type of reaction of the autonomic nervous system. The results of the Cold Pressor Test and the Schellong Test were in favor of a transient inhibitory action of opipramol on the parasympathetic nervous system, whereas the dermographic test was practically unaffected by opipramol. Clinically the tranquilizing and antidepressive action was note-worthy, but the action of opipramol on the functional disorders was remarkable.

St. Raphael University Clinic
Louvain, Belgium

2452 Denys, Walter J. *L'épilepsie cyclique. Facteurs principaux pouvant l'expliquer; illustration par le cas d'un homme dont la comitialité a été améliorée par le chlorprothixène.* (Cyclic epilepsy. Major factors by which it may be explained; illustrated by the case of a male epileptic improved by chlorprothixene therapy.) *Acta Neurologica et Psychiatrica Belgica*, 63(10):892-901, 1963.

The cyclic nature of epileptic seizures is reviewed in connection with the following factors: seasons, environmental temperature, atmospheric pressure, anaphylactic factors, state of hydration of the organism, alkalosis, degree of glycemia, psychic factors, and sensory stimuli. The cyclic nature of migraine is briefly discussed. The case history of a 68-year-old woman with epileptic seizures recurring at regular intervals is reviewed. This patient was refractory to various combinations of anticonvulsants, but improved remarkably when chlorprothixene was added to the drug regimen. The patient was receiving 30 cg phenobarbital and 20 cg diphenylhydantoin daily. Chlorprothixene was added in the following dosage schedule: 100 mg/day i.m., 50 mg/day p.o. b.i.d., and finally, 100 mg/day p.o. b.i.d. When chlorprothixene was withdrawn 3 years later, the epileptic seizures did not return, but the patient's behavior deteriorated markedly. Other refractory patients showed no dramatic improvement when chlorprothixene was added to their drug regimen.

Psychiatric Institute
Bierneux, Belgium

2453 Bobon, J., Collard, J., Delree, Ch., & Gernay, J. M. *Le Spiropéridol. (Spiroperidol.)* *Acta Neurologica et Psychiatrica Belgica*, 63(12):991-1003, 1963.

Spiroperidol (R 5147), a haloperidol derivative, was tested for its therapeutic effects on 21 psychotic patients, hospitalized an average of 10 years, ranging from 33 to 68 years of age. They had previously been treated by electrical and drug-induced shock, as well as by chlorpromazine, promazine, haloperidol, methylperidol, thioperazine, prothipendyl, and thiaxanthene; two patients had had no previous neuroleptic treatment. The dose of spiroperidol ranged from 0.2 to 50 mg; the average optimal dose was 2.9 mg/day, improvement being stabilized in the seventh week of treatment. Only six patients showed blood pressure changes, and five showed pulse changes; appetite, however, seemed to be affected in all but two cases. Side effects included sleep disorders, akinesia, akathisia, and dystonic and, in particular, extrapyramidal side effects. A comparative study of the effects of haloperidol on 14 patients yielded a high correlation between therapeutic results and extrapyramidal hypertonia. Spiroperidol may be classified as a major neuroleptic, between haloperidol and triperidol, even though this experiment failed to prove its superiority to haloperidol.

Psychiatric Clinic
University and Sanatorium Sainte-Agathe
Liège, Belgium

2454 Collard, J. & Kerf, J. *Un nouvel anxiolytique: Le Ro 5-2807 ou diazepam (A new anxiolytic: Ro 5-2807, or diazepam.)* *Acta Neurologica et Psychiatrica Belgica*, 63(12):1004-1010, 1963.

The usefulness of diazepam in neurotic states with anxiety was investigated in 32 subjects (females/males = 2/1) treated as outpatients for 1 to 8 weeks. The dosages were given p.o.: 21 patients 15 mg/day, 10 patients 10 mg/day, and 1 patient 45 mg/day. The average optimal dose was found to be 15 mg/d in three doses. The overall therapeutic effects of the drug suggested valuable chemotherapeutic use in neurotic states. The results showed 2 patients cured, very good improvement in 5 patients, moderate improvement in 13 patients, slight improvement in 10 patients, and no change in 2 patients. All results on the seven target symptoms (anxiety, psychic tension, sadness, major obsession, asthenia, affective irritability, and insomnia) were good, with the exception of an uncertain

effect in the inhibition of affective irritability. Side effects (drowsiness and ebriety), in frequency and intensity, were a function of dosage. As an antianxiety agent, diazepam is more potent than are chlordiazepoxide, meprobamate, and placebo.

Psychiatric Clinic
University of Liege
Liege, Belgium

- 2455 Arnold, O. G. & Hoff, G. **The therapy of schizophrenia.** In: Ministry of Health, U.S.S.R. Aktual'nyye voprosy psikhiiatrii i nevropatologii. (Current problems of psychiatry and neuropathology.) Morozova, G. V., ed. Moscow, 1963, p. 297-309.

The pathogenesis of schizophrenia is discussed in relation to heredity, constitution (combination of body build and the peculiarities of the main vegetative-regulatory processes), psychodynamic development of the personality, and the relationship of the patient with the environment. The origin of the symptoms of schizophrenia is connected with a disorder in the main biological functions of the brain cells, and the appearance of the schizophrenic defect is explained by the stabilization of these functions on a lower level. Studies of metabolic activities of various organs with relation to schizophrenia are presented. Initial therapy recommended included ECT or treatment with neuroleptics, and if a transition to the schizophrenic process takes place, the instituting of insulin shock. Following elucidation of the psychopathology of the case, psychotherapy with special attention to the provoking psychogenic factors is carried out. The mechanism of the insulin action is discussed. Emphasis is placed on the need for psychotherapy in all forms of schizophrenia after somatic-biological treatment has been carried out. The care of the discharged patient is the last state of therapy.

Vienna, Austria

- 2456 Naumova, V. V. **Clinico-experimental basis of the treatment of schizophrenic patients with periodic drug-induced sleep.** In: Ministry of Health, U.S.S.R. Aktual'nyye voprosy psikhiiatrii i nevropatologii. (Current problems of psychiatry and neuropathology.) Morozova, G. V., ed. Moscow, 1963, p. 310-320.

Pilot studies carried out to determine the effects of drug-induced sleep in the treatment of schizophrenics showed that 3- to 5-day periods of sleep therapy were more beneficial than a 10-day course of drug treatment. As a result, 50 male schizophrenic patients (17 to 34 years of age) were given a soporific to ascertain the drug-induced sleep effects in more detail. There were 19 patients with paranoid or hallucinatory--paranoid forms, 29 with the simple form, and 2 catatonics. The drugs and dosages used were trional and medinal 0.1 g, barbamy 0.05 g, and luminal 0.04 to 0.05 g. They were administered three to four times in 24 hours. Each course of treatment lasted for 3 to 5 days with intervals of 1 to 10 days between courses. The same drug was used in the repeated therapy unless the condition was not improved, and then the drug was changed. Sleep occurred most frequently for 12 to 13 hours. In the 29 patients with the simple form of schizophrenia, 15 were improved, and 8 of the 19 patients with the paranoid or hallucinatory--paranoid syndrome showed improvement. Of the 19 patients with hallucinatory--paranoid schizophrenia, 12 were treated in the acute stage and only 1 was cured and discharged. An improvement in behavior and a decrease in inhibition were observed in the other patients. Five of the remaining seven patients were discharged following sleep therapy. The duration of sleep was longer in the patients whose condition improved than in the patients whose condition deteriorated. Improvement occurred mainly in changes in the motor disorders and emotions. The number of courses of sleep treatment varied from two to five.

Ukrainian Scientific Research
Psychoneurology Institute
Kharkov, U.S.S.R.

- 2457 Andreyev, A. L. **Therapeutic use of certain antidepressant drugs in psychiatric hospitals.** In: Ministry of Health, U.S.S.R. Aktual'nyye voprosy psikhiiatrii i nevropatologii. (Current problems of psychiatry and neuropathology.) Morozova, G. V., ed. Moscow, 1963, p. 546-551.

After a review of related studies, a discussion is given of a study conducted to test the efficacy of imipramine on

40 patients of both sexes, who were suffering from epileptic dysphoria. These cases comprised several types of epilepsy: 7 genuine, 26 symptomatic, 4 rheumatic, and 3 traumatic. The drug was administered at an average daily dose of 200 mg. Duration of treatment ranged from 2 to 6 weeks. There was considerable improvement in all 50 patients. The drug effects were mood improvement; a calming effect; and a cessation of grief, fears, and suicidal thoughts. No side effects were observed. It was concluded that imipramine is useful in treating epileptic disorders of mood.

Moscow, U.S.S.R.

- 2458 Rokhlin, L. L. & Turovskaya, S. S.
On the efficacy of reserpine treatment of psychotic patients. In: Ministry of Health, U.S.S.R. Aktual'nyye voprosy psikhiiatrii i nevropatologii. (Current problems of psychiatry and neuropathology.) Morozova, G. V., ed. Moscow, 1963. p. 552-559.

A brief discussion of the comparative pharmacologic activity of reserpine and aminazine is presented. Reserpine was used in the treatment of 122 patients with vascular psychoses and 100 schizophrenic patients. Noticeable results were observed in hypertonic psychotic patients given small doses of reserpine (1 to 3 mg/kg/day). In patients with verbal hallucinosis of vascular origin, the dosage of the drug should be increased up to 8 to 10 mg/day using both oral and i.m. preparations. Particularly good results have been obtained in patients with cerebral atherosclerosis with the hallucinatory-paranoid syndrome. In another study, reserpine was administered in doses of 5 to 6 mg/day for 1 to 2 months in the treatment of schizophrenic patients. Very good remissions were attained only when reserpine was used either in alternation or in combination with other treatments. Half of the patients had had the disease for 1 to 5 years. A satisfactory effect was obtained in a number of the patients treated with reserpine alone. Reserpine therapy was effective in schizophrenic patients with excited mania and in patients with states of excitement combined with confusion. It is recommended that larger doses (10 to 15 ml i.m.) may be given until an improvement is noted in the patients; then the route of administration should be changed to oral administration and the dosage should be decreased 25% for

3 to 6 months. As a result of reserpine treatment, complications may appear, but these can be handled without difficulty.

Moscow, U.S.S.R.

- 2459 Szereday, Z. & Kovács, L.
Praemedication to gynaecological operations. *Therapia Hungarica*, 11:22-24, 1963.

The drugs Frenolon, Trioxazin, and Hirepin were employed to test the efficacy of premedication on 308 patients ranging in age from 18 to 68 years. Medication was administered in three successive stages before surgery: first, 0.3 g of Trioxazin t.i.d., then 10 mg p.o. of Frenolon (151 patients) and two tablets of Hirepin (157 patients), and finally (1 hour before the induction of anesthesia), 50 mg of promethazine, 100 mg of pethidine, and 0.5 mg of atropine were injected i.m. The results of premedication were good. Hypertensive patients responded better to Hirepin, and normotensive patients responded better to Frenolon. No drug side effects or complications were observed either during or after the operation. The premedication procedure proved to be beneficial, and the drugs used met the anesthesiological requirements.

Department of Obstetrics and Gynecology
Medical University of Szeged
Szeged, Hungary

- 2460 Torgyan, S. A new major tranquilizer. *Therapia Hungarica*, 11:25-27, 1963.

The effect of Frenolon was studied on 134 patients, 71 females and 63 males, with ages of 15 to 60 years, who suffered from internal diseases. Duration of treatment was from less than 1 to over 6 weeks. The patients were divided into three major groups for treatment: Group A included 58 patients suffering from gastrointestinal disorders, who received 15 mg p.o. over 2 to 10 weeks. Group B included 39 patients suffering from circulatory diseases, who received 15 to 20 mg p.o. Group C included 37 patients suffering from vegetative dystonia; 31 of these received 15 mg p.o. t.i.d., and 6 received injections of 5 mg b.i.d. Placebo was administered to 20 patients who had readily responded to Frenolon. Test

results for the three groups showed as follows: Group A, excellent improvement reported by 31 patients; Group B, good results in 27; and Group C, good results, especially in the cardiovascular patients. No improvement was noticed in 17 of the 20 placebo-treated patients. Side effects were minimal, consisting of 3 cases of Parkinsonian tremor, infrequent cases of vertigo, sluggishness of bowels, and dryness of mouth. Frenolon treatment showed good results when administered to patients who suffered from organic changes.

Balassa Municipal Hospital
Budapest, Hungary

2461 Moussong-Kovács, E. & Takács, L.
Treatment of narcolepsy with imipramin. *Therapia Hungarica*, 11:32-34, 1963.

The case histories of four narcoleptic patients who were treated with imipramine are reported. Case 1 (21-year-old male) was diagnosed as essential narcolepsy and was given 50 mg/day of imipramine, which was later reduced to 25 mg/day. In case 2 (17-year-old male), anamnesis pointed to a traumatic origin of the disease, and the patient was given 50 mg/day of imipramine. In case 3 (39-year-old female), a diagnosis of narcolepsy was added, during pregnancy, to the affective atonies that had occurred during childhood, and the patient received 50 mg/day of imipramine. In case 4 (51-year-old male), EEG and clinically verified epilepsy changed into narcoleptic attacks, and the patient was treated with 25 mg/day of imipramine. In each case the attacks of sleep disappeared immediately. The uniform pathogenesis justifies treatment with imipramine in essential and symptomatic narcolepsy.

Medical University
Budapest, Hungary

2462 Fejér, A. **Hirepin treatment of vascular headache.** *Therapia Hungarica*, 12:24-26, 1963.

The effects of Hirepin, which consists of 25 mg chlorpromazine, 0.5 mg reserpine, and 5 mg promethazine, were investigated in 65 patients (43 females) who had suffered from vascular headaches for several years. The patients were young or

middle aged. Drug administration began with very small doses of $\frac{1}{4}$ tablet in the morning, at noon, and in the evening. In the early stages of treatment, patients also received calcium acetyl salicylate one tablet t.i.d. for 2 weeks. The dose of Hirepin was increased, after 10 days, by $\frac{1}{4}$ to $\frac{1}{2}$ tablet in the morning and at noon. Most of the patients had a favorable response. Cases of cerebral sclerosis and orthostatic collapse observed in the beginning stages of treatment can be reduced by rest and caution in dosage. Hirepin treatment shows hypotensive, permeability-decreasing, analgesic, and sedative effects; it favorably influences the causes responsible for vascular headaches. Side effects consisted of slight vertigo in two or three cases, which disappeared with reduced dosage.

Department of Medicine
State Institute of Neurology and Psychiatry
Budapest, Hungary

2463 Kolodny, A. Lewis. **Controlled clinical evaluation of a new muscle relaxant—chlorphenesin carbamate.** *Psychosomatics*, 4:161-164, 1963.

This investigation, conducted as a double-blind study of 100 patients suffering from a variety of rheumatic and traumatic musculoskeletal conditions, was made to evaluate the skeletal-muscle-relaxant activity and analgesic effects of chlorphenesin carbamate. The subjects, 51 males and 49 females with an average of 42 years and an age span from 18 to 78 years, were given matching oral tablets of chlorphenesin carbamate (400 mg q.i.d.) or placebo according to a randomization allocation. Dosage was increased to 800 mg q.i.d. after 3 days if inadequate responses were noted. Medication was continued for 7 to 12 days. Statistical tests revealed definite muscle-relaxant and analgesic properties. Of the 19 patients who developed side effects (dry mouth, dizziness, insomnia, nausea, indigestion, macular rash with submaxillary gland swelling), 12 were receiving chlorphenesin carbamate. It is concluded that the drug appears to offer excellent treatment for musculoskeletal conditions involving muscle spasm and pain.

Division of Rheumatology
North Charles General Hospital
Baltimore, Maryland

CLINICAL STUDIES 2464-2467

2464 Levy, S. William. **A psychosomatic approach to the management of recalcitrant dermatoses.** Psychosomatics, 4:334-337, 1963.

The effects of diazepam as a calming agent were investigated in 151 patients (105 females and 46 males, age range 13 to 92 years, average age 40 years) with various recalcitrant dermatoses in which emotions played significant etiologic roles. The drug was administered in doses of 2.5 to 10 mg/day for a period of 2 to 17 weeks. Standard topical therapies (steroids, tars, dimethisoquin, and calamine lotion) were maintained, but there were no attempts at formal or interpretative psychotherapy. The results were good in 136 patients, fair in 8, and poor in 7. There were no signs of renal and hepatic damage, addiction, or habituation. One patient developed slight drowsiness, which disappeared with adjustment of the daily dosage. From these results, it would seem that diazepam is a safe and effective agent for controlling the emotional aspects of cutaneous disorders. The results of later study on an additional 350 patients given diazepam showed that the drug is a satisfactory aid in the management of skin disorders.

Division of Dermatology
University of California
School of Medicine
San Francisco, California

2465 Saunders, John C. **Treatment of hospitalized depressed and schizophrenic patients with monoamine oxidase inhibitors: Including reflections on pargyline.** Annals of the New York Academy of Sciences, 107:1081-1089, 1963.

Pargyline alone or in combination with a tranquilizer was given to 59 female patients (19 to 65 years of age), diagnosed as depressive, manic depressive, or schizophrenic, in order to evaluate the effectiveness of the drug in relieving depression and anergy. Pargyline alone was given to 15 patients at an initial dose of 25 mg t.i.d., which was increased to 50 mg t.i.d. if depression was not ameliorated by the third week. Significant responses were observed before 6 weeks of therapy had elapsed, and after 32 months of clinical trial, pargyline was found to be of exceptional value as an antidepressive agent. In 44 patients, a tranquilizer (phenothiazine or Rauwolfia alkaloid) was given after the fourth week of pargyline treatment. It was concluded that pargyline

is clinically one of the most effective drugs to alleviate depression, anergy autism, ambivalence, and aberrant affect in the schizophrenic patient, but the drug must be given in combination with a potent tranquilizer in order to prevent the secondary symptoms of the psychoses.

Research Facility
Rockland State Hospital
Orangeburg, New York

2466 Dunlop, Edwin. **Antidepressant effects of MAO inhibitors.** Annals of the New York Academy of Sciences, 107:1107-1116, 1963.

Evaluation of two MAO inhibitors, W3207B and pargyline HCl, was carried out in depressed patients. The W3207B was administered in doses of 5 to 45 mg/day to 21 hospitalized patients. Laboratory studies and physical examinations were performed. The average age of the group was 45 years, and the average treatment period was 5.4 weeks. The effectiveness of therapy was graded on a global four-point scale, and the degree of depression was rated during the control period and at weekly intervals during therapy by means of the BPRS. Analysis of the clinical results showed 67% were very much improved and 29% were moderately improved; there was no improvement in 4%. The drug produced a marked degree of antidepressant activity, which also diminished the mounting agitation, anxiety, and tension. The side effects were minimal. Seventy patients (29 males and 41 females) were treated with 50 to 100 mg/day of pargyline. The age range was 25 to 81 years. Half of the patients were treated on an outpatient basis, and half were hospitalized. Average duration of total treatment was 65.6 days, and onset of clinical improvement was noted as early as the second day in some. Fifty-four showed good to excellent improvement. Side effects were reported by 22, with hypotension, insomnia, and agitation being the most common. Only five patients were dropped because of side effects.

Fuller Memorial Sanitarium
South Attleboro, Massachusetts

2467 Feldman, Paul E. **Comparison of effects of 2-methyl-3-piperidino-pyrazine on target symptoms of anergic schizophrenics.** Annals of the New York Academy of Sciences, 107:1117-1130, 1963.

This paper reports the results obtained in the administration of 2-methyl-3-piperidino-pyrazine (W3207B) to a group of 61 hospitalized patients of which 55 were diagnosed

as schizophrenics (25 males and 30 females; average age, 38 years), 5 as depressive reactions (1 male and 4 females; average age, 44 years), and 1 as mentally deficient (1 female, 42 years of age). The average duration of treatment with W3207B was 93 days, and the majority of the patients received 30 to 60 mg/day. A variety of profiles of other antidepressant compounds were selected for comparison with that of W3207B because comparative data were available. On the basis of target-symptom responses (dress and personal hygiene, delusions, hallucination, negativism, hypoactivity, bizarre mannerisms, appetite, tension, etc.), W3207B seemed to fulfill the criteria for an antidepressant compound in that its effects upon hypoactivity were significant and also by the absence of any marked antipsychotic action. Such side effects as insomnia and nervousness were also in keeping with the model of an antidepressant compound. The antidepressant activity of W3207B appeared to be a manifest at dosages of 15 to 20 mg. It is believed that W3207B may prove to be particularly useful for treatment of patients in whom weight gain is undesirable.

Topeka State Hospital
Topeka, Kansas

- 2468 Popper, Robert & Prather, J. Richard.
Safety in anesthesia through drugs of short duration, propiomazine an example.
Memphis and Mid-South Medical Journal, 38:
231-237, 1963.

Propiomazine hydrochloride was tested on 103 surgical patients, 102 males and 1 female, 22 to 74 years of age, to observe its effect in the management of safe anesthesia. The drug was used only as a supplement to other premedication and anesthesia. The patients were divided into three groups for drug administration: Group A, (54 patients) received 10 to 20 mg i.v.; Group B, (42 patients) received 20 mg i.m. (1 hour before surgery); and Group C (7 patients) received 20 mg p.o. (1 to 2 hours before surgery). Results, as based upon the degree of sedation achieved, were 76 excellent, 18 good, and 1 poor. Propiomazine greatly increased and prolonged the sedative effects of morphine and pentothal sodium. Injections were most effective than were oral administration. No toxic or other serious side effects were observed. Propiomazine hydrochloride is very effective in attaining sedation of short duration in apprehensive and restless surgical patients.

Veterans Administration
Medical Teaching Group Hospital
Memphis, Tennessee

- 2469 Kraines, S. H. **A practical therapy for chronic alcoholic patients.**
Memphis and Mid-South Medical Journal, 38(12):
457-469, 1963.

The treatment of twenty-two chronic alcoholics by a combination of psychological reorientation, disulfiram, and psychotropic drugs is presented. Intoxicated and delirious patients were sedated with chlorpromazine (50 mg) or chlordiazepoxide (5 mg i.m.) before actual therapy; fluids were given i.v. along with vitamins B and C. Therapeutic medication began at least 24 hours after an alcoholic intake. It consisted of 0.5 g of disulfiram every morning, amphetamine (dextroamphetamine plus amytal) each morning, and a hypnotic at bedtime. The results were as follows: 3 were considered "treatment failures", and 19 had ceased drinking for 1 to 3 years. Case histories are given.

(No address)

- 2470 Geert-Jorgensen, Einar. **Treatment of anxiety neuroses and psychosomatic syndromes by a new Librium-metabolite: Valium.** Acta Psychiatrica Scandinavica, 11(4):218-222, 1963.

Diazepam was evaluated for its effectiveness in the treatment of 55 patients (28 males and 27 females) with anxiety neuroses and psychosomatic syndromes. In 20 of the patients (12 with obsessive-compulsive neuroses, 4 with anxiety neurosis, and 4 with constitutional asthenic neurosis), RO 4-5360 had been given previously, and the results from these patients were compared with those obtained with diazepam. The effects of both drugs were then compared to the already known effects of chlordiazepoxide. Both drugs were given in dosages of 10 mg q.i.d. initially; later, the dosage was given at 5 mg t.i.d. or q.i.d. or 5 mg t.i.d. plus 10 mg at bedtime. The action of diazepam was superior to the action of chlordiazepoxide but inferior to the action of RO 4-5360. Side effects (shivers, general debilitation, incoordination, and hallucinations) of the drugs were identical, but manifestations were less marked after diazepam. Diazepam showed no antidepressive action, and the sedative effect was inferior to that of RO 4-5360. It was concluded that diazepam may become the drug of choice in treating neurosis, but in severe cases and in cases requiring a sedative effect, RO 4-5360 is recommended.

Frederiksberg Hospital
Copenhagen, Denmark

CLINICAL STUDIES 2471-2474

2471 Perris, Carlo & Brattemo, Carl-Erik.
The sedation threshold as a method
of evaluating anti-depressive treatments.
Acta Psychiatrica Scandinavica, Supplement
39:111-119, 1963.

Determination of the sedation thresholds of 21 female patients (mean age, 42.6 years) was made before and after antidepressive treatments in order to investigate the effects of the treatment within the general framework of the sedation threshold method. The subjects were divided into two groups; those with endogenous depression (11 patients) showed low thresholds (median, 3.29 mg/kg amobarbital) and those with exogenous depression (10 patients) showed high thresholds (median, 4.55 mg/kg amobarbital). According to the results obtained from a self-rating depression scale, from the Maudsley Personality Inventory, and from the Minnesota Multiphasic Personality Inventory, it was concluded that the high threshold group was the most vital of the two groups and was the least interested in making a good impression. In psychomotor activity (the ball-and-needle test), the high threshold group showed more irregularity in performance during work. After treatment, the thresholds of both groups were raised, with a tendency toward similarity in value (median threshold, 5.0 mg/kg).

Sidsjön's Mental State Hospital
Sundsvall, Sweden

2472 Jensen, Egill & Schulsinger, Fini.
Treatment with amitriptyline (Laroxyl)
by injection. *Acta Psychiatrica*
Scandinavica, Supplement 39:244-247, 1963.

The results obtained in 20 patients (11 men and 9 women, average age, 58.9 years) treated with p.o. administration of amitriptyline were compared with those obtained in 20 patients (11 men and 9 women, average age, 51.6 years) treated with amitriptyline i.m. according to onset of action and sedative effect. The correct concentration of the injection solution was also investigated. Of the 20 patients treated with p.o. amitriptyline, 14 had endogenous depression and 6 had neurotic depression. Of those treated with i.m. amitriptyline, 12 had endogenous depression, 5 had psychogenic depression, and 3 had neurotic depression. The p.o. treatment was given in doses of 25 mg t.i.d. initially, then increased to 50 mg t.i.d. and finally reduced to 75 to 100 mg/day for 1 to 2 months. The treatment was started at doses of 25 mg t.i.d., increased to 50

mg t.i.d., then given p.o. at 50 mg t.i.d. until the time of discharge when 75 to 100 mg/day was given. Of those patients treated by injections, 50% of the patients treated orally reached the registered effect after 16 days. The local side effects of amitriptyline, in a 1% solution, probably do not play an essential part. The side effects experienced were sleepiness, indolence, vertigo, and dryness of mouth.

Kommunehospitalet
Copenhagen, Denmark

2473 Kristensen, Ketty Kjaerbye. L.S.D.
treatment in a Copenhagen department
of admission. *Acta Psychiatrica*
Scandinavica, Supplement 169:161-166, 1963.

A brief outline of a few topical points that define the author's opinion on the experience gained in LSD treatment has been given. In a group of less than 100 patients (12 to 60 years of age), about 50% of the patients presenting character neuroses (50% of the cases) improved and about 60% of the patients with other neurotic diseases (33% of the cases) improved. None of the cases of anancastic neuroses (8 patients) improved, but patients with psychotic symptoms (13 patients) showed more satisfactory results. There were four attempts at suicide, one being successful. The dosage, rarely beyond 200 µg, of LSD was adjusted according to the patients. A satisfactory contact with the nurse and therapist is of particular importance during LSD therapy. A more rigid course in LSD therapy should be followed, due to the serious complications (psychotic episodes and suicide) that have been observed.

Frederiksberg Hospital
Copenhagen, Denmark

2474 Geert-Jorgensen, Einar. Treatment of
anxiety neuroses and psychosomatic
syndromes using a new Librium-metabolite,
Ro 4-5360. *Acta Psychiatrica Scandinavica*,
Supplement 169:209-217, 1963.

A chlordiazepoxide analog, Ro 4-5360, was tested in 146 cases (49 males and 97 females, ages 17 to 74 years) for the treatment of anxiety neuroses and psychosomatic syndromes. The subjects, 58 of whom were outpatients, were given initial doses of 10 mg q.i.d., then 5 mg q.i.d., or 5 mg t.i.d. plus 10 mg

at bedtime. The drug was most satisfactory in cases of anxiety and psychosomatic neuroses. The Ro 4-5360 was very satisfactory as a sedative, especially in cases of agitated endogenous mental depressions, but possessed no specific antidepressive action. In cases of endogenous or psychogenic depressions, Ro 4-5360 may be combined with electroshock and antidepressive medication. The drug should be considered a symptomatic rather than a curative agent, and its action seems to be superior to that of chlordiazepoxide. Side effects of Ro 4-5360 (fatigue, dizziness) were most severe when given in the same doses as chlordiazepoxide.

Department of Psychiatry
Frederiksberg Hospital
Copenhagen, Denmark

- 2475 Kristiansen, Erik Sarauw.
Preliminary clinical experiences with an imipramine-metabolite, G 35020, desmethylinipramine = DMI. Acta Psychiatrica Scandinavica, Supplement 169: 234-243, 1963.

The results were reported of a preliminary clinical trial of desmethylinipramine (DMI) involving 17 patients (12 males and 5 females, 18 to 60 years of age); of the 17, 12 patients had endogenous depression, 2 had psychogenic depression, and 3 had neurotic depression. Six patients had been treated previously with other antidepressants without effect. On the first day of the trial, DMI, an imipramine metabolite, was given i.m. in a dose of 12.5 mg b.i.d., which was increased to 50 mg b.i.d. for 2 weeks. The DMI was then given p.o. at a dose of 200 mg/day until an effect was observed (usually from 20 to 50 days). All remissions that occurred were among the patients with endogenous depression. Some improvement was seen in three patients, and two patients remained unchanged. The final therapeutic effect was less pronounced for DMI than for imipramine. The side effects (sweating, headaches, fatigue, tremor) of DMI were the same and of the same quantity as the effects of imipramine; i.m. DMI was a worse local irritant than imipramine. In most cases, the antidepressant effect was observed during the first week. The emotional level was mildly affected by DMI, but there was no directly stimulating effect.

The University Hospital of Copenhagen
Copenhagen, Denmark

- 2476 Ekblom, Bengt & Lassenius, Börje.
Long-term neuroleptic treatment of chronic schizophrenic patients. Acta Psychiatrica Scandinavica, Supplement 169:333-334, 1963.

The results of a followup study of 200 schizophrenic patients (100 males and 100 females) on long-term neuroleptic treatment have been registered by cross sections after 3, 5, and 7½ years. During the first years of this study, female patients were more intensively treated, and during the latter years male patients were more intensively treated. At the 5-year control period, 12% of the women were discharged, 33% were improved, and 12% were deceased. After 5 years, 8% of the men were discharged, 23% were improved, and 11% were deceased. At the 7½-year control period, 15% of the women and 14% of the men were discharged, and 36% of the women and 41% of the men were improved. In the female group, results were better in those patients hospitalized for less than 10 years and in those diagnosed as paranoid schizophrenia than in the patients diagnosed as hebephrenics. In the male group, there was difficulty in discharging those from rural areas.

Sidsjön's Mental Hospital
Sundsvall, Sweden

- 2477 Gerle, Bo. **Observations on use of haloperidol following 3 years' experience.** Acta Psychiatrica Scandinavica, Supplement 169:348-350, 1963.

The efficacy of haloperidol in treating mental diseases is discussed. The use of the drug is indicated in cases of acute agitation, schizophrenia, senile psychosis, and hyperactivity in retarded oligophrenic patients. Dosages (given usually in the A.M.) began with 0.5 to 2 mg once or twice daily with a maintenance dose of 1 to 2 mg/day. Initial dosage in the treatment of acute agitation may be as high as 10 mg/day. The drug is often given in combination with chlorpromazine and levomepromazine. The drug may be given either i.v. or i.m. In a previous study, 91 of 175 patients showed better results with haloperidol than with other drugs. No side effects were observed at the dosages given. Haloperidol appears to be nontoxic and an extremely useful drug for treating psychoses.

St. Lars Mental Hospital
Lund, Sweden

CLINICAL STUDIES 2478-2480

2478 Lingjaerde, Odd. **Tetrabenazine (Nitoman) in the treatment of psychoses.** With a discussion on the central mode of action of tetrabenazine and reserpine. *Acta Psychiatrica Scandinavica*, Supplement 170: 7-109, 1963.

The effectiveness of tetrabenazine in the treatment of psychoses was tested in three patient groups (a total of 82 patients). In the first group of patients (25 schizophrenic women, 24 to 70 years of age), 16 who had received reserpine (2 to 10 mg) until the start of the trial and 9 who had been without treatment for 2 months prior to the trial received tetrabenazine (30 to 100 mg/day) for 8 weeks. A double-blind, cross-over trial with tetrabenazine and placebo was employed in the second group of 25 women (32 to 85 years of age), 24 of whom were schizophrenic. Tetrabenazine (25 mg t.i.d. for 1 week and 50 mg t.i.d. for the next 2 weeks) and the placebo were given in random succession for 3 consecutive weeks of each trial period. The third group (32 female patients, 21 to 81 years of age), consisting of 20 patients with schizophrenia, 5 with constitutional psychosis, and 5 with senile and presenile psychoses, was given tetrabenazine (50 to 150 mg/day p.o. or 50 to 100 mg/day i.m.) for periods of 1½ weeks to 16 months. Due to the withdrawal of the drug in five patients of the second group because of side effects, the total evaluation involved only 77 patients. The therapeutic effect in the 77 patients was as follows: complete remission 47%, marked improvement 17%, slight improvement 40%, no change 35%, and worsening 4%. The rate and quality of improvement was highest in the third group. The improvement occurred within 2 weeks and appeared chiefly as a normalization of the effects. The optimal p.o. dosage seemed to be about 25 to 50 mg t.i.d. The patients with the shortest duration of illness and those classified as paranoid schizophrenics showed the best results. Side effects occurred in 48% of the patients, most commonly as drowsiness in 25%. Akathisia was seen in four patients, dyskinesia in three, severe parkinsonism in two, and depressive reactions in two patients. From these results and from the results of 21 clinical investigations on more than 1,300 psychotic patients, it was concluded that tetrabenazine has a moderate unspecific sedative-hypnotic effect, a marked ataractic effect, and a marked antipsychotic effect. Tetrabenazine is preferred to reserpine in chronic schizophrenia, but the effect may not be as stable and as lasting as that of reserpine. In cases of hallucinosis and paranoia, better results may be obtained

with tetrabenazine, whereas cases of restlessness and overactivity may react better to chlorpromazine. (98 references)

Oslo, Norway

2479 Matlin, Edwin. **Use of chlordiazepoxide in obese patients.** *Clinical Medicine*, 70(4):780-784, 1963.

A clinical study to test the efficacy of chlordiazepoxide and *α*-amphetamine was conducted on 42 obese patients, 35 women and 7 men, whose mean age was 40 years. They had no overt symptoms of emotional disorders. All the patients were overweight by 10% to 25% or more, and were placed on a 1,000-calorie diet. A 5-mg capsule of chlordiazepoxide and a 5-mg tablet of *α*-amphetamine t.i.d. were prescribed, to be taken 1 hour before meals. The study lasted 10 weeks. The following results were evaluated in percentages of weight loss: 29 from 10% to 15%, 6 from 15% to 25%, and 7 less than 10%. Thirty-five patients lost from 10% to over 25% of their initial weight. No side effects were observed even on dosages, in some instances, of 5 to 10 mg b.i.d. The majority of patients voluntarily continued this dietary therapy until achievement of their normal weight. The two drugs are effective in achieving smooth weight reduction.

Garden City, New York

2480 Lamphier, Timothy A. **Use of promethazine in medication of surgical patients.** *Clinical Medicine*, 70(5):954-956, 1963.

The effectiveness of promethazine in the medication of surgical patients was investigated in 1,124 patients. Promethazine (25 mg i.m.) was given preoperatively and every 4 hours postoperatively (50 mg i.m.). Results were assumed to be good if apprehension was decreased and if the patient reached the operating room in a light sleep. The results of preoperative medication were good in 71%, fair in 25%, and poor in 4%. Response to postoperative medication was good in 84%, fair in 13%, and poor in 3%. The dosages of meperidine and scopolamine was reduced to one-half the usual dosage, and scopolamine was not used in 60% of the patients. The side-effects (nausea and vomiting, drug rash, diarrhea) were not serious; all subsided after a decrease of

dosage. It was concluded that promethazine is an excellent adjunct to preoperative and postoperative therapeutics.

Boston, Massachusetts

2481 Settel, Edward. Combined *d*-amphetamine and chlordiazepoxide therapy in the emotionally disturbed obese patient. *Clinical Medicine*, 70(6):1077-1088, 1963.

A series of 72 patients (60 women and 12 men, median age, 37.5 years) suffering from obesity (10% to 25% overweight) associated with emotional disturbance were treated by an integrated program of simple psychotherapy and diet reduction (800 to 1,000 calories/day) coupled with supportive medication in the form of *d*-amphetamine as an anorexiant and chlordiazepoxide as an inducer of greater emotional stability. Each tablet, given t.i.d. 20 to 60 minutes before meals, contained 5 mg of *d*-amphetamine sulfate and 5 or 10 mg of chlordiazepoxide. A clinically significant fall in weight was achieved in 66 patients, 47 of whom showed excellent weight loss (10% to 15%) and 19 of whom showed good weight loss (26%). The rate of weight loss and the gross weight loss were directly proportional to the degree of initial overweight. According to the severity of the condition, the emotional factors were well controlled by a dosage of 15 or 30 mg/day of chlordiazepoxide. It was concluded that this drug combination provided a safe and effective supportive therapy in the management of obesity complicated by emotional disturbances.

Forest Hills, New York

2482 Kline, Nathan S. Use of pargyline (Eutonyl) in private practice. *Annals of the New York Academy of Sciences*, 107:1090-1106, 1963.

Pargyline was tested for its effectiveness in the relief of depression and related symptoms in 50 subjects (38 females and 12 males) with a relatively low expectancy of therapeutic response. The dosage was usually 25 mg t.i.d., and the maintenance dose was 25 mg/day. Of the 50 patients, 15 responded with satisfactory relief of depression. In seven patients, there was marked improvement but inadequate followup data. In another seven patients, results were favorable but

intolerable side effects developed. In 21 patients, unsatisfactory results were obtained. Most of the patients who did develop intolerable side effects had done so previously on other medication, and in a number of cases, the patients tolerated pargyline better than they had other similar preparations.

Research Facility
Rockland State Hospital
Orangeburg, New York

2483 Goldhahn, W. E. & Otto, P. Zur extrakorporalen Hämodialyse von Barbitursäuren. (Extracorporeal hemodialysis of barbituric acid derivatives.) *Arzneimittel-Forschung*, 13(11):977-980, 1963.

Experiments were performed with an artificial kidney reproduced on a scale one-tenth the size of the clinical model to determine the time taken by various barbiturates to pass through the cellophane membranes of the apparatus. Barbitol sodium, phenobarbital sodium, and 5-ethyl-5-crotylbarbituric acid were tested. The contents of the cellophane tubules were sampled every 10 minutes during the 90-minute dialysis period, and samples were analyzed by ultraviolet spectrophotometry. There was very little difference in the dialysis time of the three barbiturates. About three-fourths of the drugs dialyzed out within 40 minutes; almost one-third dialyzed during the first 10 minutes.

Medical Academy
Erfurt, Germany

2484 Brown, Allan S. Neuroleptanalgesia. The present position for neurosurgery. *Irish Journal of Medical Science*, 6(455):535-540, 1963.

The techniques for neuroleptanalgesia are described, and the application of this method and its advantages are illustrated from studies of 65 patients undergoing operations for Parkinson's disease and 100 patients subjected to a variety of radio-diagnostic procedures, as well as several other major and minor surgical operations. In the first method, the patient who has continued to take his anti-Parkinson drugs is sedated one-half hour before the operation by slow i.v. injection of 2 to 3 mg of dehydrobenzperidol followed by 2 to 3 mg of phenoperidine. For radio-diagnostic investigations, 4 to 5 mg

of dehydrobenzperidol is injected slowly i.v., followed by 4 to 5 mg of dextrometamide. This method is suited to those operations that demand the retention of consciousness and full cooperation with excellent sedation.

Department of Surgical Neurology and Anesthetics
University of Edinburgh
Edinburgh, Scotland

2485 Alnaes, Randolph & Kristiansen, Juel. *Desmethylinipramino (Pertofran) i behandlingen av depresjoner. En klinisk og psykodynamisk vurdering. (Desmethylinipramine (Pertofran) in the treatment of depression. A clinical and psychodynamic analysis.)* Nordisk Psykiatrisk Tidsskrift, 17(5):425-436, 1963.

The therapeutic effects of desmethylinipramine (DMI) were compared with those of imipramine. A brief review of the pharmacology and the mode of action of DMI and imipramine is given. Thirty-two female inpatients with depressive states of various etiology were given DMI for 3 weeks in a maximal daily dose of 50 mg t.i.d. Twenty-four patients improved; only three patients needed ECT. Of 21 patients diagnosed as endogenous, constitutional, or involutional depressives, 18 improved. Patients with pronounced asthenic conditions were refractory. Compared to imipramine, DMI had a faster onset of action and fewer side effects. It is probable that DMI, the imipramine metabolite, is responsible for imipramine's antidepressant effect.

Lier Hospital
Lier, Norway

2486 Velloso, Fernando Megre & Paprocki, Jorge. *Ensaio clínico em torno de um novo neuroléptico do grupo das butirofenonas. (Clinical study of a new neuroleptic of the butyrophenone group.)* O Hospital, 63(6):215-222, 1963.

The therapeutic effects of the butyrophenone haloperidol were tested in 50 female psychotics, 18 to 71 years of age. Treatment was begun at 1 mg/day p.o., increasing by one 1-mg tablet/day; half of the patients received increasing doses until therapeutic responses were seen, and the other half received increased dosages until saturation symptoms appeared. Patients refusing oral administration were given 5 mg haloperidol i.v. daily, followed by i.m. treatment b.i.d., and then oral treatment.

During the period of observation, the minimum daily dose was 2 mg and the maximum was 20 mg; maintenance dosage was 3 to 6 mg/day. Duration of treatment averaged 30 days. Parenteral administration resulted in immediate sedation of all patients with psychomotor excitation, regardless of nature or intensity. This was followed by gradual attenuation of aggressiveness, autistic and negativistic behavior, hallucinations, delirious ideation, and confusion. No side effects were observed, and laboratory tests revealed no toxic effects.

Galba Velloso Hospital
Belo Horizonte, Minas Gerais, Brazil

2487 Corsino, G. M. & Rebusci, G. G. *Su un caso di psicosi allucinatoria periodica: Efficacia della terapia imipraminica. (A case of periodic hallucinatory psychosis: Efficacy of imipramine.)* Rivista Sperimentale di Freniatria e Medicina Legale delle Alienazioni Mentali, 87(1):145-154, 1963.

A case is reported of the successful use of imipramine in the treatment of acute hallucinatory psychosis. The subject, a 28-year-old male, had previously suffered two acute hallucinatory attacks that had been completely relieved by ECT and insulin shock therapy. The third attack was precipitated by cranial trauma suffered in a motorcycle accident. The patient was given 150 to 200 mg chlorpromazine daily for 40 days with not relief of symptoms. Imipramine therapy was then initiated, with doses increasing to a maximum of 300 mg daily after 14 to 15 days. Dosage was then reduced to 150 mg daily p.o. Within 20 days, there was complete remission of all psychic manifestations. The patient is being maintained on 75 mg imipramine daily p.o.

Clinic of Neurological and Mental Diseases
University of Bologna
Bologna, Italy

2488 Barbeau, André, Sourkes, Théodore L., & Murphy, Gerard F. *Les catécholamines dans la maladie de Parkinson. (Catecholamines in Parkinson's disease.)* In: de Ajuriaguerra J., ed. *Monoamines et système nerveux central (Monoamines and the central nervous system.)* Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 247-262.

In an attempt to confirm the hypothesis, predicting a catecholamine metabolic disorder in Parkinson's disease, a study was made of

69 patients in various stages of Parkinson's disease. The controls used were 31 hospital employees and 20 schizophrenics. Rigidity and trembling were clinically evaluated in the face and extremities, and each patient was given a battery of physical tests, including 14 tests for rigidity and 3 tests for trembling. Urinary catecholamine analysis of the 24-hour urine samples of 31 normal subjects and 30 parkinsonian patients showed the dopamine excretion totals of the parkinsonian patients to be considerably below those of normal patients. Several factors (degree of mobility, urinary volume, type of disease, and principal symptoms) evidently can influence the results of the catecholamine analysis. In 30 patients with Parkinson's disease and in 20 schizophrenics with the Parkinson syndrome due to phenothiazines, the MAO inhibitor, tranylcypromine (10 mg t.i.d.), produced about a 40% improvement, in each group, over the initial condition. In 6 patients with Parkinson's disease, α -methyldopa aggravated tremor and slightly modified rigidity. In a double-blind study, L-DOPA, tyrosine, and tranylcypromine showed that the immediate precursors of dopamine have a clear effect on rigidity. All these experiments seem to confirm that a catecholamine metabolic disorder occurs in Parkinson's disease.

Laboratory of Neurological Sciences
University of Montreal
Montreal, Canada

2489 Grant, George H. **Chlordiazepoxide used for apprehensive dental patients: Preliminary observations.** *Journal of the American Dental Association*, 66:182-185, 1963.

This report discusses the effects of chlordiazepoxide in 56 dental patients (5 to 50 years of age), selected because of their histories of exaggerated fear and tension. Single doses of 5 to 25 mg of chlordiazepoxide were given 1 hour before treatment. Responses were excellent in 46 patients and good in 8, whereas 2 patients failed to show beneficial effects. The drug was well tolerated, and side effects were not noted. A few patients were given 10 mg at bedtime the night before the office visit and 20 mg before treatment. Eleven of the cases considered to be representative are discussed in detail. It is concluded that the apparently unusual emotional states of the patients may have enhanced the value of the simple clinical observations presented.

11 Chester Drive
Rye, New York

2490 Wolf, Robert L., Mendlowitz, Milton, Mizgala, Henry, & Kornfeld, Peter. **Clinical evaluation of pargyline hydrochloride, (a new monoamine oxidase inhibitor), in primary hypertension.** *Journal of the Mount Sinai Hospital, New York*, 30:151-155, 1963.

The antihypertensive effect of pargyline HCl in 27 patients with primary benign hypertension was investigated for a 9-month period, which was preceded by two biweekly control periods in which the subjects received placebo medication. Thirteen of the subjects were severely hypertensive (blood pressures above 190 mm Hg systolic and 120 mm Hg diastolic); 10 were mildly hypertensive (blood pressures above 150 mm Hg systolic and 100 mm Hg diastolic); and 4 were moderately hypertensive (intermediate criteria). The average therapeutic dose was 50 mg. A good result was shown in 16 patients, and a fair result was obtained in 6 patients. Of the 16 who showed good results, 7 were mildly hypertensive, 2 were moderately hypertensive, and 7 were severely hypertensive. Nausea was the most frequent side effect, noted in eight patients, and postural hypotension with dizziness was seen in six patients. The results of this study support the use of pargyline HCl as an effective MAO inhibitor and antihypertensive agent in man.

Department of Medicine
The Mount Sinai Hospital
New York, New York

2491 Chepkii, L. P. **Kliniko-fiziologicheskoye obosnovaniye primeneniya trankvilizatora andaksina v khirurgii shchitovidnoy zhelezy. (Clinico-physiological basis for the use of the tranquilizing agent Andaxin in thyroid surgery.)** *Problemy Endokrinologii i Gormonoterapii*, 9:98-101, 1963.

Meprobamate was given to 42 patients who were suffering from a thyroid disease, and who had worsened after an intake of neurological drugs. The patients were given an average dosage of 0.4 g meprobamate. Twenty-two patients underwent a clinico-physiological examination within 2 to 2½ hours after the intake of the drug. The results of the study showed that meprobamate produced a normalizing effect on the hemodynamics and external respiration. It also produced marked hypometabolic effect and reduced the oxygen uptake without any significant depression of other external respiration indexes. The drug produced a reduction in the intensity of the metabolic processes and, therefore, a decrease in the cardiovascular exertion,

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a pulse rate reduction of 10 to 20 beats in 27 patients, and some drop of the arterial pressure. The effect of meprobamate on the vegetative-trophic indexes was not pronounced. Meprobamate may be recommended, in conjunction with analgetics, hypnotics, and other pharmacological preparations, as an effective and harmless means for the preoperative medication of patients with thyrotoxicosis.

Dnepropetrovsk Medical Institute
Dnepropetrovsk, U.S.S.R.

2492 Cohen, Sidney. **Excretory patterns clinical response to the tablet and prolonged-action forms of thioridazine.** Proceedings of the Western Pharmacology Society, 6:65-67, 1963.

In order to explore whether any clinical relationship exists between the tablet form and the prolonged-action form of thioridazine, 85 chronic schizophrenic patients who had been on thioridazine tablets (average daily dose, 647 mg) for 2 to 10 months were randomly selected for this study. The patients were switched from the tablet to the thioridazine spacetab. The dosage records, reviewed monthly for 7 months, showed a gradual decrease in the amount and time of medication. Most of the patients needed spacetab only once a day, and eight patients took it only 5 times/week. At the end of the 7-month period, the average daily dose was 480 mg.

Wadsworth GM & S Hospital
Los Angeles, California

2493 Ghosh, Shanti. **Nialamide in the treatment of mental retardation.** Indian Journal of Child Health, 12:347-349, 1963.

Nialamide was tried in 32 mentally backward children (17 males and 15 females) in doses of 25 to 100 mg/day for a period of 4 to 8 months. The age incidence of the subjects who had satisfied the criterion of a moron, was as follows: below 1 year, 2; 1 to 5 years, 18; and above 5 years, 12. Apart from the initial increase in alertness, responsiveness, and improved appetite, no further improvement was noted, and the performance of the children did not improve significantly. No toxic effects of the drug were recorded.

Irwin Hospital
New Delhi, India

2494 Montani, S. & Perret, Cl. **Le traitement de l'intoxication barbiturique. (Treatment of barbiturate poisoning based on 271 cases.)** Schweizerische Medizinische Wochenschrift, 93(19):692-695, 1963.

The therapeutic results are reported in 271 cases (74% females) of barbiturate intoxication treated between 1957 and 1962 by forced diuresis and provoked alkalization of the blood. The criterion of severity was based on the condition of the patient on arrival at the clinic, in three degrees of increasing severity: Group I, 125 patients; Group II, 108 patients; and Group III, 38 patients. The overall mortality was 0.7% (two patients in Group III, cardiac arrest) for the group as a whole. Respiratory complications occurred in 88 cases, but were alleviated by treatment with respiratory analeptics (prethamid, Remeffline). Bronchopulmonary complications in 30 patients was corrected by repeated rinsing and postural drainage. External massage corrected cardiac arrest in four patients. Urinary infection due to catheterization occurred in eight patients. It was concluded that this treatment (Scandinavian method) has minimal risks.

Medical Clinic
University of Lausanne
Lausanne, Switzerland

2495 Morris-Owen, R. M. **"Cover-dose" management of contact sensitivity to chlorpromazine.** British Journal of Dermatology, 75:167-169, 1963.

The case of a 31-year-old woman, exposed to chlorpromazine daily, who developed chlorpromazine contact dermatitis is reported, and successful desensitization is described. On alternate days, she was given p.o. doses (1 μ g, 2 μ g, 4 μ g, 8 μ g, and 12 μ g) of chlorpromazine without reaction. A mild reaction developed at 18 μ g, and the next doses (24 μ g, 30 μ g, 36 μ g, and 42 μ g) were increased by smaller ratios and produced no further reaction. She continued taking 42 μ g/day as a cover dose and handled chlorpromazine frequently. About 6 months later, the dose was cut to 18 μ g/day, and 1 month later the drug was withdrawn completely with no further relapse.

Radcliffe Infirmary
Oxford, England

- 2496 Fujita, Bunkichi. (A case of adverse seizure.) Brain and Nerve, 15:499-502, 1963.

The case is reported of a 30-year-old male who had "adverse seizure" and a cystic malformation opening into the ventriculus lateralis and located in the right parietal lobe. The seizure usually accompanied parietal symptoms and occasionally led to typical epileptic attacks. Bemegride provoked a simple grand mal attack only, but when it was combined with LSD-25, typical adverse seizure was observed. Similar cases are discussed and compared with this case.

(No address)

- 2497 Gooch, J. M. Carisoprodol in cerebral palsy: A controlled trial. Developmental Medicine and Child Neurology, 5:603-608, 1963.

Assessment of the therapeutic effectiveness of carisoprodol in the treatment of 17 children with various types of cerebral palsy was made. A double-blind study comparing the effect of carisoprodol (700 to 1,750 mg/day) amylobarbitol (25 mg/day), and a placebo was carried out. During the 14-week trial, each child received a course of each of the three tablets in sequence. At the end of each week, information on the child's progress was obtained from the mother and therapists. A final report was requested after the child had been off the drug for 1 week to see if there were any withdrawal symptoms or evidence of relapse. No significant progress was made, and no consistent amelioration was seen in the children at the time of drug administration. The only side effect was drowsiness, which was reduced or disappeared through acquired tolerance to the drug. In most of the children, progress had slowed down or ceased.

Cerebral Palsy Clinic
Royal Children's Hospital
Melbourne, Australia

- 2498 Berkowitz, Donald. The use of chlordiazepoxide as premedication in patients prior to gastroscopy. American Journal of Gastroenterology, 40:525-527, 1963.

Chlordiazepoxide (50 to 100 mg i.m.) was administered to 35 patients (19 males and 16 females, 24 to 66 years of age) prior to gastroscopic examination. In 28 of the

patients, the drug produced excellent relaxation, enabling the procedure to be carried out with no difficulty. The medication appeared less effective in four patients, but the examination was accomplished. However, in three cases endoscopy was not successful.

Department of Gastroenterology
Hahnemann Medical College and Hospital
Philadelphia, Pennsylvania

- 2499 Saarne, A. Experiences with haloperidol (Haldol) as a premedicant. Acta Anaesthesiologica Scandinavica, 7:21-30, 1963.

To evaluate the effects of haloperidol for premedication, 1,163 patients (634 men and 529 women, 18 to 90 years of age) were treated with haloperidol before surgery. Haloperidol was administered in the following three ways: (1) A total of 963 patients received 5 mg i.m. on the day of the operation. (2) A total of 100 patients received 2.5 mg the evening before the operation and 2.5 mg on the morning of the operation. (3) A total of 100 patients were given 2 mg p.o. the evening before surgery and 2 mg p.o. on the morning of the operation. Anesthetics given included barbiturate- N_2O -curare, halothane, and "anesthetic blockade." Satisfactory or good results occurred with the premedication methods used in the first and second groups (94%), and with the method used in the third group (88%). The maximal effect of haloperidol was reached in 45 to 60 minutes and was maintained at a fairly constant level until after the operation, which in some cases was several hours later. No deleterious effects were observed on the course of the operation or on the anesthesia. No complementary sedation during the operation was required for patients given "anesthetic blockade." The drug produced a psychic indifference and removed the patient from emotional and sensory stimuli. The antiemetic effect of haloperidol premedication was significant. In patients with increased muscle tonus and organic disorders of the CNS, haloperidol is contraindicated. Extrapyramidal symptoms appeared in two patients.

Department of Anesthetics
Centrallasarettet
Vänersborg, Sweden

- 2500** Robie, Theodore R. **Anti-depressant drug combinations.** Journal of the Medical Society of New Jersey, 60(12):547-554, 1963.

The use of antidepressant drugs alone or in combination have proven valuable in the treatment of depressive patients, either in making them amenable to psychotherapy or in avoiding suicidal attempts. Stop-gap euphoriant therapy may be accomplished by methylphenidate. Combined methylphenidate and iproniazid was used successfully in the treatment of a case of melancholia. Chlordiazepoxide in combination with isocarboxazid, nialamide, or phenelzine has been used in the treatment of the most extremely agitated type of melancholia. A case is presented of a malnourished female patient who became quite depressed. She was started on a regime of combined antidepressant, appetite stimulating and hypervitamin therapy and gained 10 pounds the first month. More than 2 weeks elapsed before the melancholia began to disappear. She received supportive psychotherapy with isocarboxazid, methylphenidate, and nortriptyline. Another case of acute melancholia with psychosomatic colitis and hypertension is discussed. The patient was treated successfully with phenelzine and iproniazid, along with seconal and medication for colitis. An illustration is given of a toxic reaction to amitriptyline. It is advisable not to give more than 6 mg of amitriptyline the first time. Intravenous therapy of 12 to 16 mg/day with the oral dosage is helpful for severe anxiety hysteria. Dextroamphetamine (2.5 mg) may be used with imipramine or amitriptyline (12 mg or less) to augment the antidepressant effect. A discussion of the use of pargyline (12 to 15 mg/day) in the treatment of two patients is presented. The aim of all chemotherapy or ECT in psychiatric illness is the enhancement of psychotherapy.

676 Park Avenue
East Orange, New Jersey

- 2501** Sicuteri, F. **Prophylactic treatment of migraine by means of lysergic acid derivatives.** Triangle; Sandoz Journal of Medical Science, 6:116-125, 1963.

The assumption is made that in spontaneous migraine attacks, the so-called precipitating factors (psychic, gastrointestinal, and atmospheric factors) become active via the same pathogenetic mechanism, the vasomotor system. A definite interrelationship exists between blood vessel changes and pain and nervous symptoms, all of which may be caused by an excess of the

tissue hormones that govern conditions in the small blood vessels. Since 5HT has a marked effect on the blood vessels and nerves and may cause severe pain, several lysergic acid derivatives with strong antiserotonin action were given to 390 patients. Among the drugs administered were LSD 25 (50 µg to 100 µg), BOL 148 (2 to 4 mg), LAE 32 (*α*-lysergic acid ethylamide---1 to 3 mg), PML (1-methyl-*α*-lysergic acid propanolamide---1 to 3 mg), and UML 491 (methysergide---2 to 6 mg). The therapeutic effects of methysergide were presented in detail. The drug should be administered initially in small doses ($\frac{1}{2}$ mg p.o.) with gradually increasing doses up to 3 to 8 mg/day within 7 to 10 days, and maintained for 1 to 2 months. It is beneficial in the treatment of vascular syndromes, headache of vascular origin, Horton's syndrome, and "cluster headaches." In 33% of the cases treated, the attacks ceased and in another 33% they decreased in number. Contraindications are pregnancy, cardiac, renal, and liver insufficiency, and angina pectoris. Side effects reported were nausea, vomiting, euphoria, epigastric pain, erethism, and depression. However, many of these effects diminish or disappear with continued therapy and adjusted dosage. Reserpine ($\frac{1}{4}$ or $\frac{1}{2}$ mg i.v.) frequently precipitates a migraine attack. In cases of vascular headaches, reserpine (0.10 to 2 mg i.v.) may prove beneficial.

Clinic of General Medicine
University of Florence
Florence, Italy

- 2502** Wilson, David O., Hall, Jack H., & Dennison, A. D. **An evaluation of mebutamate (Capla).** Journal of the Indiana State Medical Association, 56:876-881, 1963.

A discussion of animal experiments carried out to determine the mechanism of action of the antihypertensive drug mebutamate and its toxicity is presented. In a study using two dogs, it was found that the blood pressure rise usually associated with the stimulation of certain areas of the medulla and hypothalamus could be counteracted by mebutamate. In mice, the LD₅₀ is 550 mg/kg. In 28 normal adults given mebutamate (300 mg q.i.d. for 56 days), no significant changes were observed in the laboratory studies. Two subjects reported inability in controlling their gait. Fourteen women patients (41 to 70 years of age) with mild hypertension were studied by means of a double-blind technique.

Mebutamate (300 mg q.i.d. or a placebo was given. The average blood pressure of all the participants completing the study was 176/103. After four blood-pressure readings were obtained, the patients were switched. Each patient took the drug for a minimum of 2 months. Seven of the 10 patients who completed the study took chlorothiazide or hydrochlorothiazide throughout the study. The only significant differences in blood pressure occurred in systolic pressures taken in the sitting position, which were decreased by mebutamate. There were no postural hypotension and no differences in blood pressures taken while standing. Eight patients experienced side effects. Three had severe reactions, mainly incoordination. Drowsiness occurred in over half the patients but disappeared in some patients while on the same dosage.

Department of Internal Medicine
Methodist Hospital Graduate Medical Center
Indianapolis, Indiana

2503 Hunter, C. D. & Weiner, Ben.

Results with oxymetholone elixir in a group of depressed women. Southwestern Medicine, 44:211-212, 1963.

The efficacy of oxymetholone was tested on 50 depressed females, 19 to 62 years old, whose duration of symptoms ranged from 5 to 5½ months. The patients were classified into two groups---mildly depressed (29) and moderately depressed (21). Nine patients had organic pathology. An elixir (2.5 mg/5 cc) was given in one teaspoon t.i.d. after meals. Treatment lasted for 90 days. No other medications were given, except for an analgesic in four cases. Test results showed that 64% of all the women improved, with 76.9% of the "mildly" depressed and 47.7% of the "moderately" depressed being improved. An average weight increase of 2.6 lbs/month was observed in 46 women. The majority of women (82%) liked or preferred the drug in the elixir form. Only two patients developed side effects; one developed urticaria and the other had nose bleeds. Both patients became asymptomatic within 48 hours after stopping the drug. The drug did not affect BUN, SGOT, or BSP values in 15 patients. Oxymetholone elixir proved to be beneficial in treating depressed women.

800 Montana Street
El Paso, Texas

2504 Hay, Rankin K. **The management of intractable pain due to advanced malignant disease.** Winnipeg Clinic Quarterly, 16:24-32, 1963.

Various medications and surgical procedures used in the treatment of pain due to advanced malignant disease are discussed. Analgesics are more effective if given before an attack of pain is fully developed; these drugs are valuable provided they are given regularly and frequently. Three categories of analgesics are delineated: the milder, most useful ones are acetylsalicylic acid, phenacetin, and phenylbutazone. The intermediate group contains codeine, methadone, and dipipanone, and the most potent ones are morphine and the alkaloids of opium. A new drug, dextromoramide, has analgesic properties with few side effects. A listing is presented of the drugs that potentiate analgesics. Because of its troublesome side effects, morphine is not suitable for prolonged use. Surgical measures, with the exception of leucotomy, are concerned with the interruption of nerve pathways that conduct pain impulses to the sensorium. Section of a mixed peripheral nerve is practicable only in a limb and is rarely justified. Posterior rhizotomy is of value for relief of pain in the face, head, or neck, as well as in the trunk and perineum, but produces loss of normal bladder and bowel function. Chemical rhizotomy is not selective and damages all types of sensory and motor fibers that it contacts. Spinothalamic tract section provides satisfactory and permanent relief of pain in the contralateral trunk and leg and should be done while the patient is ambulatory. Leucotomy is only justified when a direct attack of the pain conducting pathway is impracticable and when no other type of psychotherapy controls the excessive emotional response to the pain.

(No address)

2505 Linn, Evelyn & Reiss, Frederick.
Itching dermatoses treated with combined dexbrompheniramine-fluphenazine. A double-blind comparison with trimeprazine.) Skin; Dermatology in General Practice, 2:374-376, 1963.

A double-blind study to evaluate the usefulness of combined dexbrompheniramine (6 mg) and fluphenazine (0.5 mg) in the treatment of 77 adults (13 to 80 years of age) with chronic types of pruritic dermatoses was carried out. The reference drug was a sustained-action capsule containing 5 mg of trimeprazine. The dosage of both drugs was 1 capsule b.i.d.

CLINICAL STUDIES 2506-2508

for 1 week. Clinical evaluation was made prior to the trial and after drug administration. Of the 46 patients who received the test drug, a partial to complete relief of pruritus was noted in 80.5%. Among the 31 patients who received trimeprazine, a fair to good response was observed in 64.5%. Somnolence and fatigue were the only side effects reported by the patients receiving the test drug. One patient receiving trimeprazine had to be dropped because of pronounced fatigue.

870 Fifth Avenue
New York, New York

- 2506 Santucci, Peter A. **Treating depression as a decrease in functional capacity.** Maryland State Medical Journal, 12:546-552, 1963.

Several uncomplicated, inventory-type questionnaires were used in 70 patients (51 women and 19 men, average age, 41.2 years) undergoing treatment (psychotherapy and phenelzine 45 mg/day) for depression. Prior to treatment, the subjects were used to obtain a profile of depressed patients and to determine whether certain emotional, mental, and physical functions are affected. After treatment, the pretreatment and posttreatment responses to the Current Symptomatology Check List and MMPI were tabulated and analyzed in an effort to measure overall changes in functional capacity of the patients. Manifestations of depression were interpreted as being either emotional, mental, or physical in nature. The results showed that 59 patients were considered to have shown satisfactory improvement (marked in 32 and significant in 27). Comparison of pretreatment and posttreatment responses to the Current Symptomatology Check List was generally indicative of improvement in functional capacity. Emotional symptoms were decreased to a greater extent than either mental or physical symptoms. A comparison of the pretreatment and posttreatment results on the MMPI test was indicative of improvement in outlook and functional capacity. Side effects, with the exception of hypotension, occurred in less than 5% of the patients, and, for the most part, were easily overcome by adjusting the dosage of phenelzine. A discussion of the values and shortcomings of the tests utilized in this study and a theoretical explanation for the development of depression are presented.

Holy Cross Hospital
Silver Spring, Maryland

- 2507 Johnson, William A. **Long-term trifluoperazine therapy in a schizophrenic patient.** Northwest Medicine, 62:884, 1963.

Long-term studies of the use of trifluoperazine in the treatment of schizophrenic patients are discussed. A case report of a 34-year-old schizophrenic treated for 37 months with trifluoperazine (15 to 20 mg/day) with no untoward effects is presented. From this and other studies, it would appear that long-term therapy with this drug is possible safe. However, in a following note, a report is cited of the occurrence of extrapyramidal symptoms, skin eruption, jaundice, agranulocytosis, and allergic purpura.

1417 15th Avenue
Longview, Washington

- 2508 Mostert, J. W. **A centrally acting relaxant in anesthesia.** South African Journal of Medicine, 37:1281-1284, 1963.

A method of surgical relaxation (in the presence of unimpaired spontaneous respiration during general anesthesia) made possible by guaiacol glyceryl ether (MY 301) is described. The chemical structure of MY 301 is similar to that of mephenesin. The critical concentration of MY 301 for the production of hemolysis was 12.5%. The drug was given to 117 patients (average age, 45) who had various types of operations. The average dose for the production of fair to good abdominal relaxation in an adult was 4 to 6 g (80 to 120 ml of 5% My 301). Small amounts of ether or halothane were given in addition to MY 301 in abdominal operations to achieve better relaxation. The MY 301 reduced the amount of anesthetic required. The main utility of the drug appeared to be in extraperitoneal operations. The action of MY 301 reaches its peak in 10 to 15 minutes and is completely over in 20 to 30 minutes. Sudden recovery and alertness of the patients after receiving MY 301 occurred. Relaxants and anesthetics of all types were potentiated by MY 301. The only side effect was hypotension, which was a result of overdosage of the drug.

Johannesburg Hospital and
University of the Witwatersrand
Johannesburg, South Africa

- 2509** Macris, Spyros G., Macris, Gerasimos J., Cacouri, Alexandra N., & Karapiperis, Spyros N. Intravenous methylphenidate for the treatment of singultus. *Anesthesia and Analgesia*, 42(4): 440-442, 1963.

In order to evaluate the therapeutic effectiveness of methylphenidate (20 mg i.v.) in the treatment of singultus, 58 patients (57 males and 1 female, 15 to 86 years of age) were treated with the drug 96 times. Singultus occurred most frequently during operation and general anesthesia, and postoperatively. The frequency of attack ranged from 1 every 3 seconds to 1 every 4 minutes. A control group of 15 patients with singultus received a placebo injection (normal saline). Singultus ceased in 93 of the 96 times the drug was given but recurred 55 times. The cessation of singultus occurred either during injection or between 30 seconds and 5 minutes after the injection. Singultus ceased in only four of the patients receiving the placebo.

Anesthesia Department
Army Pension Hospital
Athens, Greece

- 2511** Ono, Kazuo, Motizuki, Akira, Turuoka, Takoto, & Misu, Hidesuke. (Clinical effects of thioproperazine in the treatment of chronic schizophrenics, especially on the intermittent treatment method.) *Japanese Archives of Internal Medicine*, 10:345-356, 1963.

Thioproperazine was given to 61 chronic schizophrenics who had been refractory to all previous therapy. Three treatment methods were used: daily dosage of thioproperazine in increasing amounts; thioproperazine combined with chlorpromazine or levomepromazine; and twice weekly dosage with thioproperazine. Initial dosage for the first two methods of treatment was 5 mg (3 mg if possible) t.i.d.; dosage for the intermittent-treatment method was 10 mg. The intermittent method proved most effective. Thioproperazine was particularly effective in relieving mutism, negativism, and apathy. Side effects included parkinsonian symptoms, autonomic nervous involvement (salivation, cold sweat, and blushing), anxiety, disorientation, and insomnia.

Japanese University
School of Medicine
Tokyo, Japan

- 2510** Hardy, William, Ten Pas, Andrew, & Nixon, Robert K. Meprobamate intoxication treated by peritoneal dialysis: Report of a case. *Henry Ford Hospital Medical Bulletin*, 11:347-350, 1963.

A case is reported of a 49-year-old man who had ingested eighty 400-mg meprobamate tablets and seven 200-mg amobarbital and secobarbital capsules in a 1-hour period. Hypotension and respiratory and CNS depression were noted on admission to the hospital. Initial treatment consisted of gastric lavage, i.v. fluids, and maximal i.v. levartenerol. Bemegride (100 mg i.v.) had no appreciable effect. Approximately 8 hours after admission, peritoneal dialysis was instituted with the patient in an agonal state. There was dramatic improvement over the following 12 hours. Peritoneal dialysis was discontinued after 24 hours, and the patient's main complaints were weakness and numbness of the left foot. When discharged 10 days later, he was still weak. A discussion is presented of the side effects, toxicology, and mode of action of meprobamate.

Henry Ford Hospital
Detroit, Michigan

- 2512** Nadel, M. B. J. Psychoanalytic and neurovegetative mood depressing and elating treatment of depressions and psychoses. *Acta Neurovegetativa*, 25:332-338, 1963.

A new and original casual treatment of mild and severe depressions and psychoses by the combined psychoanalytic and neurovegetative mood depressing and elating treatment has been presented. In depression there is the vagotonic depressive influence of the psychic apparatus of the patient, manifested by slowed psychomotor activity, slow monotonous voice, general depressed appearance with expressed helplessness and hopelessness, and suicidal and homicidal thoughts. The new depressing and elating therapeutic approach is advantageous due to the shortness of the treatment period, a better result in those depressions refractory to the known antidepressant medication or to ECT, and a better accessibility of the diseased condition to ECT and to psychotherapy.

(No address)

CLINICAL STUDIES 2513-2515

2513 Sweeney, Ralph E. Oral treatment of skeletal muscle spasm: A double-blind clinical study. *Current Therapeutic Research*, 5(6):305-309, 1963.

A double-blind clinical evaluation was made of oral therapy with combined orphenadrine--fluphenazine on 85 patients, 12 to 67 years old, who had acute and chronic musculo-skeletal disorders. Treatment duration was 5 days. The patients were given, in a random manner and in a prescribed dosage, either a tableted orphenadrine--fluphenazine combination (100 mg orphenadrine citrate and 0.5 mg fluphenazine dihydrochloride) or control tablets of 100 mg orphenadrine citrate. The prescribed dosage was 1 tablet b.i.d. The 35 patients treated with the control drug showed the following results: 32% little or no improvement, 31% moderate improvement, and 17% marked-to-complete improvement. The 50 test-drug patients showed the following results: 20% little or no improvement, 30% moderate improvement, and 50% marked-to-complete improvement. The test-drug patients had no serious side effects, those noted being drowsiness and nervousness. Seven of the control group patients complained of mild nausea. Orphenadrine--fluphenazine therapy was more effective than orphenadrine alone in alleviating painful muscle spasm or stiffness.

550 Chilton Street
Elizabeth, New Jersey

2514 Narvaez, Guillermo Calderon. Hidroxyfenamato, un nuevo medicamento en contra de la ansiedad. (Hydroxyphenamate, a new anxiety controlling drug.) *Revista de Neurologia-Neurocirugia-Psiquiatria*, 4(2):1-8, 1963.

Hydroxyphenamate, a nonphenothiazine tranquilizer, was investigated in 30 patients (22 females and 8 males, 19 to 52 years of age) with a diagnosis of anxiety (simple in 12, associated with depression in 10, with hypochondria in 4, reactive anxiety in 2, obsessive compulsive in 1, and paranoid psychosis in 1) for its utility as an anxiety-controlling drug. Various tranquilizers, including meprobamate and chlordiazepoxide, had been ineffective in all patients, except for two who had received no previous treatment. Hydroxyphenamate started with 600 to 800 mg/day, was reduced to 400, 200, and 100 mg/day, and was then withdrawn. The duration of treatment was 15 days to 4 months. The results were excellent in 5 patients, good in 14,

moderate in 5, and slight in 6 patients. Side effects were reported in six cases: drowsiness in three, nausea in two, and dry mouth in one. Hydroxyphenamate was longer acting than chlordiazepoxide and shorter acting than meprobamate.

Sanatorio Psiquiátrico
Cholula, Mexico

2515 Narváez, Guillermo Calderón & Sánchez, Eduardo García. Levomepromazine en trastornos del sueño. (Levomepromazine in sleep disorders.) *Revista de la Facultad de Medicina*, 5(3):195-202, 1963.

Levomepromazine as a useful agent in sleep disorders was investigated in 50 cases (10 males, 40 females; 23 to 62 years of age). The various diagnoses included: anxiety neurosis, 17 patients; primary insomnia; 13 patients; depressions, 8 patients; barbiturate addiction, 4 patients; cervical spondylitis, 4 patients; and psychosis, 4 patients. Overall results showed good improvement in 33 patients, moderate improvement in 7 patients, and slight improvement in 10 patients. Best results were obtained in those with neurotic anxiety (92%) and in those who had been ill for less than 1 month (83%). Addiction showed 75% improvement; insomnia showed 53% improvement; and psychosis, spondylitis, and depression showed 50% improvement. Side effects reported were drowsiness in five cases and dry mouth in four cases. It was concluded that the drug facilitates sleep due to its blockage of the factors that stimulate the reticular substance, such as stimuli coming from the cortex and some hormones and enzymes, with secondary depression of its ascending stimulant action.

Pabellón Central
Manicomio General
Mexico, D. F.

See also: 2406, 2408, 2410, 2413, 2416, 2421, 2423, 2424, 2429, 2434, 2435, 2440, 2441, 2618, 2629, 2639

SIDE EFFECTS

- 2516 Rowan, Robert L. & Howley, Thomas F.
Premature ejaculations. Fertility and Sterility, 14(4):437-440, 1963.

The treatment of premature ejaculations, which can cause great anxiety, sexual impotency, and sterility is discussed. Difficulty in treating premature ejaculation stems from the fact that the condition is a symptom and not a disease entity per se. The underlying physiological pathology and psychiatric causes must be understood before adequate treatment can be undertaken. The treatment consists of prostatic massage when indicated, psychotherapy, and the use of tranquilizers. Cystoscopy and other traumatic urological procedures should be avoided unless there is some basic urologic disease. Anesthetic ointments are of no value and may produce greater anxiety.

Urological Section
 St. Vincent's Hospital
 New York, New York

- 2517 Jacobziner, Harold & Raybin, Harry W.
Accidental chemical poisonings.
Imipramine hydrochloride intoxication. New York State Journal of Medicine, 63:1394-1397, 1963.

Complete histories of several incidents of drug poisonings reported to the New York City Poison Center are presented. The use of vitamin K should be guarded. Poisoning occurred in children and adults with the following overdose of drugs: imipramine (1,000 mg) taken by a 4-year-old girl; Lindane tablets taken by a 2-year-old boy; glutethimide (5 to 12 g) ingested by a 72-year-old man in a suicidal attempt; phenindamine tartrate (250 mg) ingested by a 15-month-old boy; eight tablets of barbiturate combination (10 mg methamphetamine and 64.8 mg phenobarbital in each tablet) ingested by a 3-year-old girl; and half a bottle of salicylamide (liquid aspirin) taken by a 2-year-old boy. The salicylamide apparently was not poisonous, but was treated as such. The side effects of imipramine were dyspnea, cyanosis, convulsions, and coma with abnormal

laboratory findings. Treatment consisted of gastric lavage, i.v. fluids, amobarbital, paraldehyde, and procainamide. Lindane produced drowsiness, vomiting, and muscular twitchings; studies of the blood and urine revealed abnormalities. Treatment consisted of electrolyte balance maintenance, calcium, and phenobarbital. Peritoneal and hemodialysis were used in the glutethimide poisoning. Phenindamine side effects were vomiting, tachycardia, and tremulousness. Phenobarbital was the treatment used. The barbiturate combination produced convulsions and over excitement. Treatment was i.m. phenobarbital.

Poison Control Center
 City of New York Department of Health
 New York, New York

- 2518 Bell, Douglas B., II. & Scaff, John.
Fatal reaction to tranlycypromine (Parnate). Hawaii Medical Journal, 22(6): 440-441, 1963.

A case report is presented of an 18-year-old girl who had been under a psychiatrist's care for about a month for depression and had ingested approximately 17 tranlycypromine tablets (10 mg) with suicidal intent. She was given meperidine (75 mg i.m.) to sedate her before arrival at the hospital. Twenty minutes later, the patient experienced fever, sweating, and decerebrate rigidity. About 2 hours after admission to the hospital, clonic movements of the arms and face began. She was given phenobarbital (2 grains i.m. and 1 grain i.v.) with no effect. The laboratory studies were essentially normal. Salicylates and external cooling had no effect on the patient's temperature, which remained at 108° F, nor did i.v. norepinephrine raise the blood pressure. The patient expired 6½ hours after admission. Autopsy revealed congestion of the lungs, brain and

SIDE EFFECTS 2519-2522

kidneys, and blood in the bowels. Microscopic examination showed early gastrointestinal mucosal necrosis, cloudy swelling of the liver parenchyma and renal tubules, and hemorrhagic pulmonary edema.

Dickson-Bell Clinic
Honolulu, Hawaii

- 2519 Pisciotto, Anthony V. Some comments on the pathogenesis of agranulocytosis. Wisconsin Medical Journal, 62:230-232, 1963.

As a possible mechanism of agranulocytosis following chlorpromazine treatment, the effect of this drug was studied on the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) by bone marrow cells. Since cells actively synthesizing DNA or RNA incorporate tritiated thymidine or uridine, respectively, with resultant radioactivity, it is possible to determine the cell population capable of synthesizing DNA and RNA by counting the radioactive cells after the addition of tritiated thymidine or uridine to an incubation mixture of bone marrow and test drugs. The radioactive cells were identified by the varying number of grains over the nuclear area. It was found that chlorpromazine specifically and directly inhibited nucleic acid synthesis in bone marrow cells of sensitive persons and in 75% of a random hospital population. No such inhibition was observed in marrow preparations obtained from persons while who, on high doses of chlorpromazine, did not develop agranulocytosis. Nonmyelotoxic drugs, such as aspirin, promethazine, diphenhydramine, and penicillin, had no inhibitory effect.

Department of Internal Medicine
Marquette University School of Medicine
Milwaukee, Wisconsin

- 2520 Busch, K.-Th., Busch, G., & Lehmann, W. Zur Frage von Netzhautdegeneration nach Anwendung hoher Phenothiazindosen in der Psychiatrie. (The question of retinal degeneration after employment of high phenothiazine doses in psychiatry.) Klinische Monatsblätter für Augenheilkunde, 143(5):743-749, 1963.

Ophthalmological studies were made of 363 psychiatric patients who had been treated with varying doses of phenothiazine (primarily chlorpromazine and promethazine) to determine

any macular degeneration. Duration of phenothiazine treatment ranged from 2 to over 36 months. Dosages ranged as follows: 166 patients received from 50 to 150 mg daily; 163 patients, 150 to 250 mg daily; and 34 patients, over 250 mg daily. Of the 363 patients, 351 showed no eye changes. Six patients showed fundus changes with marked myopia, changes in dilation, and pigment accumulation. A degenerative lesion of the retina was found in only one case, a 52-year-old woman.

Brain Research Institute
Karl Marx University
Dresden, Germany

- 2521 Barton, Russell. "Toxic side effects" of drug usage. Mental Hospitals, 14:654-655, 1963.

A discussion is presented of the psychological side effects produced by paraldehyde, barbituric acid derivatives, and phenothiazine derivatives in patients with psychiatric disorders. Some of the psychological toxic effects of drug usage are: (1) Patients develop apathy toward a distressing environment. (2) No additional help is provided if the drug fails. (3) Doctors, nurses, and the patients expect miracles from the pills.

Severalls Hospital
Colchester, Essex, England

- 2522 Eckhardt, William F., Jr. Cervicallingual-masticator myoclonus. A reaction to a non-halogenated phenothiazine. Connecticut Medicine, 27(9):561, 1963.

A case report is presented of a 13-year-old white girl who was given thiethylperazine dimaleate for the treatment of mild nausea and vomiting secondary to viral gastroenteritis. She received four tablets of 10 mg each for 3 days. On the third day, the patient developed marked jaw myoclonus, extensor spasms of the cervical neck muscles, and uncontrollable upward elevation of both eyes. The patient was given 100 mg of secobarbital i.v., which brought about immediate disappearance of the tonic spasms and eye deviations.

The Stamford Hospital
Stamford, Connecticut

- 2523 Homer, LeRoy. **Methdilazine intoxication.** Journal of the Medical Society of New Jersey, 60(3):115-116, 1963.

A case is presented of a 44-year-old man who ingested 280 mg of methdilazine with a suicidal intent. The man suffered from the following side effects: severe CNS depression, labored respiration, respiratory tract obstruction (due to edema of the tongue and laryngeal structures), and gastric irritation that caused hemorrhagic gastritis and vomiting. Upon admission to hospital, treatment consisted of the following: continuous gastric suction by means of a Levine tube, i.v. infusion of 5% glucose in H₂O, alternating with 5% glucose in saline, and 1 g of caffeine sodium benzoate i.m. Two hours later, the following treatment was given: 0.55 cc of 1 to 1,000 epinephrine s.c. and 25 mg of prednisolone i.v. A tracheotomy was performed 9 hours after admission. The patient fully recovered after 13 days of hospital treatment.

150 Green Street
Woodbridge, New Jersey

- 2524 Pokras, Norman M. & Kingsbury, B. C., Jr. **Extrapyramidal reactions to prochlorperazine and similar antiemetic drugs.** Oral Surgery, Oral Medicine and Oral Pathology, 16:1261-1265, 1963.

A review is presented of the reaction of the extrapyramidal system to prochlorperazine and similar antiemetic drugs, along with a case involving a 24-year-old male patient's reaction to this drug. The intake of 10 mg of prochlorperazine i.m. b.i.d., produced the following side effects in the patient within 2 days: an extensor spasm of the neck and back muscles, loss of speech, and spasm of the masticatory muscles. Successful treatment of these reactions consisted of 0.5 mg of scopolamine injections i.v. Prochlorperazine was discontinued, and the patient improved.

2036 N. Broadway
Santa Ana, California

- 2525 Hanson, I. Rivers, Baker, Robert Lee, & Gallaher, James P. **Problem weight gain in "wanted" versus "unwanted" pregnancies.** Medical Annals of the District of Columbia, 32(12):496-497, 1963.

A double-blind study, conducted on 50 pregnant women who were gaining weight rapidly, compared the average weight gains in "wanted" (28 patients) and "unwanted" (22 patients) pregnancies after anorectic treatment that was begun in the second trimester between the 14th and the 20th week. Each patient took either placebo (lactose) or an anorectic (15 mg of *d*-amphetamine and 7.5 mg of prochlorperazine) each day. Of the 31 patients who completed the drug treatment (2 discontinued it because of preeclampsia), 89% of those who wanted pregnancy (17 patients) felt that the drug controlled their appetite, whereas 78% with unwanted pregnancy (14 patients) felt that it did not. Only 18% reported satisfactory appetite control with placebos. Eight of the 13 with marked stress in the "wanted" group became less tense and more stable; only 3 of 13 in the "unwanted" group became less tense. Overstimulation was reported by two patients and fatigue was reported by two others. Of the 51 babies born, 1 was stillborn, 1 died shortly after delivery, and 1 abnormality occurred in 1 infant (mass under the right nipple). It was concluded that weight control was independent of emotional improvement since the tensions of an unwanted pregnancy were not relieved, and weight control measures were successful.

Peninsula General Hospital
Salisbury, Maryland

- 2526 Gordon, Walter. **Photosensitivity. A report of cases and a clinical review.** South African Medical Journal, 37: 1159-1162, 1963.

Five cases of photosensitivity are described. One case (a 38-year-old colored man) was that of chronic polymorphous light eruptions. Another case (a 25-year-old colored male) was that of contact photodermatitis involving coal tars. Two cases (a 55-year-old male and a 17-year-old male) involved psoriasis in which light sensitivity was a contributing factor. The remaining case was that of a 53-year-old female who was taking dexamphetamine and trifluoperazine capsules and developed drug photosensitization. All of the cases were cleared up when the patients were confined to shaded areas.

Groot Schuur Hospital
Cape Town, South Africa

SIDE EFFECTS 2527-2528

2527 Antoni, A. A., Van de Mark, T. B.,
Gajda, J., & Weinberg, S.

**Severe, intoward reaction to perphenazine
in a patient undergoing oral surgery:
Report of case.** Journal of Oral Surgery,
Anesthesia and Hospital Dental Service,
21:246-250, 1963.

See also: 2407, 2439, 2450, 2510

A case report is given of a 32-year-old white man who underwent surgery for a prognathic mandible. He was given pentobarbital sodium i.v. and a local anesthetic on the day of admission. Surgical anesthesia was thiopental sodium i.v. and succinylcholine chloride. During surgery, nitrous oxide--oxygen and trichloroethylene were administered. Following surgery, the patient was given 4 mg of perphenazine p.o. b.i.d. for nausea and as a sedative. On the second postoperative day the patient developed a rash. Penicillin was discontinued, and the patient was given 50 mg diphenhydramine HCl. On the fifth day, he had breathing difficulty, a spasm of facial, perioral, and neck muscles, and complete obstruction in breathing. An emergency tracheotomy was performed and the patient recovered except for recurring muscle spasms in the face and neck. After discontinuation of perphenazine treatment, the spasms ceased, and the patient's recovery was uneventful.

Doctor's Hospital
Toronto, Canada

2528 Ishikawa, Toshio. (On the effect of
addiction and tolerance observed from
brain waves in animals, with special reference
to continuous administration of morphine and
methamphetamine.) Folia Pharmacologica
Japonica, 59:187-205, 1963.

The changes of the EEG patterns during a continuous 5-week administration of morphine and methamphetamine were studied in the rabbit by means of implanted electrodes. In morphine-treated animals, tolerance developed. The EEG showed arousal patterns, and the animals became sensitive to auditory stimuli. In methamphetamine-treated animals, no tolerance developed, but the EEG showed such abnormal patterns that slow waves and fast waves appeared periodically. The animals did not become sensitive to auditory stimuli. In morphine-treated animals, recovery to normal conditions occurred in 2 weeks after the drug was terminated, whereas it took 3 weeks for the methamphetamine-treated animals to return to normal.

(No address)

BEHAVIORAL STUDIES

2529 Anaesthesia Laboratory, Harvard Medical School, Massachusetts General Hospital. Manifest anxiety, amphetamine and performance. Weitzner, Martin. Boston, 1963, 14 p. Contracts USPH-M-987 and DA-49-193-MD-2136, unclassified report.

pursuit rotor test. However, the amphetamine groups performed significantly better than the placebo groups.

The Anesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital Boston, Massachusetts

Experiments were performed to study the relationship between Taylor Manifest Anxiety Scale (MAS) score and paired-associates performance in a design that required each subject to learn both a competitive and a noncompetitive paired-associates list, to explore the relationship between MAS score and performance on other tasks, and to determine whether the administration of amphetamine alters performance in ways consonant with drive theory. Ninety-six subjects were divided into three groups according to low, middle, and high MAS scores. They were further subdivided into groups of 16 each, in which half of the subjects in each group received amphetamine (14 mg/70 kg body weight) and half received a placebo prior to the experimental session. The tests included paired-associates learning, digit-letter coding, pursuit rotor test, and amphetamine and paired-associates learning. Eight test orders were used; two subjects received each order within each group of 16 subjects. No significant interactions were found between test order and MAS score and between test order and drug effect. The results showed that the high MAS scoring subjects performed better than the low MAS scoring subjects on noncompetitive paired-associates lists, but the low MAS scoring subjects are superior on competitive lists. The performance of the amphetamine groups was superior on the noncompetitive list but inferior on the competitive one. The only significant effect within the digit-letter coding data was the superiority of the three amphetamine groups when combined with the three placebo groups combined on the simple test. The high MAS scoring subjects tended to be superior on the simple test and inferior on the difficult test. No significant differences among the three MAS groups were found in the

2530 Adey, W. R. EEG studies of hippocampal system in the learning process. In: *Physiologie de l'hippocampe*. (Physiology of the hippocampus.) International Conferences of the National Scientific Research Center, August 24-26, 1961, Montpellier, France, p. 203-224. Contract AF 49(638)-686 and USPHS Grant B-1883, unclassified report.

Patterns of slow-wave activity in the hippocampal system of cats and monkeys have been studied in the course of learning certain discriminative motor performances. Simultaneous records have also been obtained from cortical and deep structures during behavioral training. Each training procedure has involved a discriminative motor performance, with testing of recent memory and long-term aspects of retention, as required in T-box performances. Certain very regular trains of waves at approximately 6 cps appeared in dorsal hippocampal areas and in the entorhinal cortex during the approach to the food reward. Administration of psychotomimetic and hallucinogenic cyclohexamine drugs (1 to 3 mg/kg) abolished all regular slow-wave activity in hippocampal structures, and loss of learned behavioral performance coincided with disruption of hippocampal and entorhinal 6-cps bursts of slow waves during the attempted approach. Rhythmic slow-wave discharges occurring simultaneously with those in the hippocampal system during the discriminative performance were noted in extrahippocampal structures, including subthalamus, rostral midbrain reticular formation and primary visual and somatic cortical areas. Small subthalamic lesions produced major changes both in behavioral performance simultaneous EEG records during the learned discrimination. On the basis of these findings, integration

of information at the cellular level may occur on the basis of these ubiquitous and pervasive wave processes. The individual neuron might function as a phase comparator, sensitive to the complex patterns of waves in both space and time sweeping across its surface, and with the possibility that its responsiveness to a particular pattern may have been influenced in subtle ways by its previous participation in similar patterns. As a more direct approach to the problem of the function of the electrotonic generators responsible for the wave process in dendritic structures, an impedance-measuring technique has been initiated, using microvolt measuring signals in animals.

University of California at Los Angeles
Los Angeles, California

2531 University of Wisconsin. Special report on drugs and sensory-feedback analysis in space science. Smith, Karl U. Madison, 1963, 43 p. Contract/Grant AF-AFOSR 61-56, unclassified report.

A progress report is given concerning efforts to apply sensory-feedback methods of behavioral analysis to pharmacological studies and environmental research in order to determine the effects of tranquilizing drugs on prenatal and infant development and on aging in man and animals. Experiments were performed to analyze brain neurohormones in developing animals and to determine the effect of drug depletion of brain neurohormones in development and aging, using reserpine to deplete brain catecholamines. Instrumentation systems for the automatic recording and analysis of the following types of activity are described: drinking and eating in young animals; eye movements in young animals and man; and speech patterns. Sensory-feedback systems for analysis of maturation and aging processes and of the effects of environment and drugs are discussed.

Psychology Department
University of Wisconsin
Madison, Wisconsin

2532 Jefferson Medical College. Neuropharmacologic profile of psychotomimetic activity. Progress report, Baker, Walter W, Philadelphia, Pennsylvania, 1963, 17 p. Contract DA 18-108-CML-7069, unclassified report.

A neuropharmacological analysis of the actions of tremorine and its active metabolite, oxotremorine, is reported that includes the differentiation of the rage and tremor responses, extensive mapping of drug-induced EEG changes in subcortical brain areas, and effects on motor reflexes. Oxotremorine was 100 times more active than tremorine in inducing the rage response. Tremor was differentiated from rage by administering chloralose and reserpine. Both depressants accentuated tremor; chloralose abolished rage, but reserpine did not. Chlorpromazine and trifluoperazine suppressed both tremors and rage. The effects of tremorine and oxotremorine on recruiting and activation and suppression of hippocampal strychnine foci and their projections are discussed. The hippocampal foci could be reactivated by strychnine or pentylenetetrazol. Physostigmine and neostigmine produced cholinergic effects similar to those of tremorine, but increased rather than decreased the focal discharge rates. The effect of oxotremorine on CNS evoked potentials is reported. Limbic evoked responses that were depressed by oxotremorine were restored by atropine. Tremorine effects on various reflexes are described. The report also includes abstracts of three papers on related topics.

The Jefferson Medical College of Philadelphia
Philadelphia, Pennsylvania

2533 Gershon, S. & Bell, C. A study of the antagonism of some indole alkaloids to the behavioural effects of "Ditran." *Medicina Experimentalis*, 8:15-27, 1963.

In an attempt to further elucidate the biological activities responsible for antagonism to JB 329 (a mixture of the *N*-ethyl piperidone and *N*-ethyl methyl pyrrolidine derivatives of phenyl cyclopentyl glycolate) the antagonism produced by yohimbine, ibogaine, harmine, piperoxan, and phenoxybenzamine against JB 329-induced behavioral activity was studied in unrestrained adult mongrel dogs (10 to 20 kg in weight). The effects of the antagonists against atropine were also determined. Drug dosages were as follows: 0.5 mg/kg JB 329; 1.0 µg/kg atropine sulfate; 0.5 mg/kg yohimbine; 1.25 mg/kg harmine;

1.75 mg/kg ibogaine; 0.25 mg/kg piperoxan HCl; and 0.25 mg/kg phenoxybenzamine HCl. Injections were given via the cephalic vein of the forelimb. The antagonists were given 30 minutes after JB 329 or atropine, when central disturbances were at their peak. Spontaneous behavior was recorded before and after drug injection. All three indoles showed antagonism to JB 329, with yohimbine producing the strongest effect. All three indoles produced some antagonism to atropine, but the degree of antagonism was lower than that seen against JB 329. Of the adrenergic blocking agents, only piperoxan produced antagonism (30% to 60%). Results were compared to those obtained with 1,2,3,4-tetrahydro-5-amino acridine HCl, and theories as to possible modes of action of these antagonists are discussed.

University of Melbourne
Parkville, Australia

2534 Giurgea, C., Moeyersoons, F., & Van Der Auwera, A. Action of some anti-motion sickness drugs on central nystagmus. *Medicina Experimentalis*, 9:361-370, 1963.

The effects of 1-benzhydryl-4-[2-(2-hydroxy-ethoxy)ethyl]piperazine HCl (UCB 1402), chlorpromazine, BS 6534, and diphenhydramine on central nystagmus were tested in 36 rabbits (2.5 to 3.0 kg in weight) with regular, constant nystagmus produced by electrical stimulation of the diencephalon according to the method of Lachmann, Bergmann, and Monnier (1958). Drugs were injected into the marginal ear vein in the following doses per kg body weight: 50µg, 100µg, 500µg, 1µg, and 2 mg UCB 1402; 2 and 4 mg diphenhydramine; 2 mg BS 6534; and 50µg, 100µg, 1.5 mg, and 2 mg chlorpromazine. The BS 6534, UCB 1402, and diphenhydramine depressed the nystagmus with a concomitant elevation of the stimulation threshold. Chlorpromazine had a biphasic action at 2 mg/kg. The clinical and physiological significance of these results is discussed.

Union Chimique Belge
Brussels, Belgium

2535 Dews, P. B. Monoamines and conditioned behavior. In: de

Ajuriaguerra, J., ed. *Monoamines et système nerveux central. (Monoamines and the central nervous system.)* Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 143-151.

A discussion is presented of the role of behavioral studies in animals in the study of drug action. Studies are reported on the effects of adrenaline, isoproterenol, *dl*-metanephrine, *dl*-normetanephrine, and mescaline on operant behavior in pigeons (weighing about 0.5 kg). The behavioral conditioning was on a reinforced fixed-interval schedule. The specific response was a peck by the pigeon delivered to a plastic key and the consequence of maintaining it was occasional delivery of food. In general, drugs were given at the end of the first cycle (9 minutes before reillumination of a plastic key), and observation was continued for five cycles (1 hour and 40 minutes). Doses of 30µg to 100µg of *L*-adrenaline caused a reduction in responding; the effect increased with increasing dose. Comparison of the activity of *L*-adrenaline with *L*-noradrenaline and *d*-isomers showed that *L*-noradrenaline had about one-third the potency of *L*-adrenaline and both *d*-isomers had about one-tenth the potency. Isoproterenol had considerable activity and so did mescaline, but neither metanephrine nor normetanephrine had appreciable activity. Pretreatment with phenoxybenzamine (1 mg) and phentolamine (1 mg) antagonized the behavior suppressing effect of *L*-adrenaline. Dichloroisoproterenol (1 mg) had no antagonistic action but there was an indication of enhancement of *L*-adrenaline effect. Iproniazid (10 mg) had no detectable effect when given alone, but enhanced the effect of *L*-adrenaline. Cocaine (0.3 mg) caused slight enhancement but showed no tendency to enhance the effects of *L*-adrenaline. Reserpine (1 mg) had a profound effect on behavior, but it is doubtful that the effect of *L*-adrenaline was changed by reserpine action. Atropine and *L*-adrenaline (100µg) reduced responding to the same extent but the effects of the pattern of responding were different. A discussion of the behavioral effects of the monoamines and their mechanism of action is given.

Department of Pharmacology
Harvard Medical School
Boston 15, Massachusetts

- 2536 Elkes, J. **Amines in relation to behavior: Some problems and approaches.** In: de Ajuriaguerra, J., ed. *Monoamines et système nerveux central.* (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 153-166.

The role of the amines in relation to behavior in man is discussed, with special emphasis on the problems involved in relating observable behavior in the intact animal to chemical changes in the brain. The following three topics are discussed: inferential evidence for the role of the amines in behavior from the intact organism; inferential evidence from studies of the brain, including neuroanatomical and neurophysiological considerations and distribution patterns of amines; and regional economy and metabolic compartmentalization within the brain in relation to behavior. (90 references)

Saint Elizabeth's Hospital
Washington, D.C.

- 2537 Wallgren, Henrik & Arvola, Alpo. **Influence of alcohol on the general activity of mice. A study of mice when undisturbed and when subjected to noise.** *Annales Medicinæ Experimentalis et Biologiae Fenniae*, 41:88-92, 1963.

The effects of a moderate dose (3 mg/g) of alcohol on the general activity of mice for 1 hour following its administration was studied under undisturbed conditions and during exposure to an irregularly recurring, intense rattling noise. Albino Swiss-Webster mice, 12 males and 12 females, 8 months of age, were used in the experiments. When activity following administration of water was used as reference, no changes in total activity were observed under undisturbed conditions in alcohol-treated mice. Noise radically changed the activity patterns of the mice. The changed pattern was normalized to a significant degree after the administration of alcohol.

The Research Laboratories of the
State Alcohol Monopoly
Helsinki, Finland

- 2538 Milligan, Marilyn M. & Kalman, Gabor. **A selective method for the study of drug effects on behavior.** *Proceedings of the Western Pharmacology Society*, 6:7-8, 1963.

Experiments, in which the conditioning paradigm utilizes a shock as a nonaversive stimulus, were carried out to determine the effect of morphine (5, 10 and 15 mg/kg) on the response of rats. One group of rats was trained with light as the discriminative stimulus. At the lower dose levels, morphine produced an increase in intertrial responding in animals for whom shock was the cue. A general depression of behavior was seen at the 15 mg/kg dose level. In experiments using light as a cue, morphine produced a dose dependent reduction in responding in the animals. No change was observed in intertrial responses. A second set of experiments was designed to compare the effects of varying actual stimulus intensity with the results obtained with morphine in rats trained with the shock-as-cue paradigm. Intertrial responding increased as the shock level decreased so that at zero the maximum number of intertrial responses was obtained. Both intertrial and reinforced responding decreased as the shock level was raised above the training level. In the nondrugged state, the animals performed most efficiently. Morphine shifted the distributions of responses so that a greater number of responses were emitted at higher shock levels. Morphine (15 mg/kg) also produced a general depression behavior in these animals.

Department of Pharmacology
Stanford University
School of Medicine
Palo Alto, California

- 2539 Petrova, J. & Topolcan, O. **Preliminary data on psychoses originated under the effect of cycloserine.** *Ceskoslovenska Psychiatrie*, 59(1):20-23, 1963.

Case histories of several tuberculin patients treated with cycloserine (500 mg/day to a maximum of 87.75 g total) are discussed with relation to the psychoses that developed as a result of this drug. The psychoses in the majority of patients disappeared spontaneously without any more specific therapy, but in a few cases, chlorpromazine (200 to 450 mg/day)

or levomeprazine were used to block the psychotic action of cycloserine. There are two phases observed after the administration of cycloserine. The first phase is characterized by vegetative disorders accompanied by increased psychomotorism, and the second phase, which does not always appear, is the delirium state. Caution is stressed in the use of this drug.

(No address)

- 2540** Kong, Tsou. (Effects of morphine upon several types of operant conditionings in the rat.) *Acta Physiologica Sinica*, 26(2):143-150, 1963.

The effects of morphine on higher nervous activity were studied in rats using five types of operant conditioning: fixed interval; variable interval; discriminative conditioning; multiple schedule (alternate fixed interval and fixed ratio); and avoidance conditioning. The principal effect of morphine was to lower the response rate. In the fixed interval schedule, involving a conditioning to time interval, there was a shortening or elimination of the initial pause, indicating that this type of conditioning was very susceptible to morphine. In the multiple schedules, morphine showed no selective action on the fixed-interval component; the response rate of both components was lowered. The differentiation in discriminative conditioning was not affected. After tolerance developed, morphine often increased rather than lowered the response rate.

Institute of Materia Medica
Academia Sinica
Shanghai, China

- 2541** Chamberlain, T. J., Rothschild, G. H., & Gerard, R. W. **Drugs affecting RNA and learning.** *Proceedings of the National Academy of Sciences of the United States of America*, 49:918-924, 1963.

In order to determine whether learning phenomena can be affected by drugs that have a profound effect on RNA metabolism, 284 Holtzman, male, albino rats (250 to 400 g in weight) were studied in three behavioral situations following drug administration. In the experiments on

spinal-cord fixation, one group of animals was injected with 50 to 200 mg/kg of 8-azaguanine i.p. prior to making cerebral lesions by ablation or electrolytically. Another group was injected with 8 to 15 mg/kg of U-9189 (1,1,3-tricyano-2-amino-1-propene) i.p. prior to the development of postural asymmetry by lesions, and another group was given 8 mg/kg of U-9189 i.p. for 4 consecutive days before the lesions were made. The 8-azaguanine clearly prolonged the time interval for fixation of the postural asymmetry in the spinal cord from 45 to 70 minutes. The spinal-cord fixation process seemed to be disrupted in the U-9189 animals injected on the day of the experiment. The animals receiving four injections of U-9189 showed the fixation time to be shortened to 30 minutes. The second experiment, avoidance conditioning, consisted of four groups of animals. One group received 8-azaguanine (50 mg/kg), and another group received 15 mg/kg of U-9189. There were control groups for each. The U-9189 was superior in the retention testing, but there was no difference between the other three groups. Drug administration groups were the same for the Hebb-Williams maze as for the avoidance conditioning experiments. The animals, however, were 15% below their projected body weight. There was no significant difference between any of these groups in performance. A discussion of the possible role of RNA in learning is presented.

Mental Health Research Institute
Ann Arbor, Michigan

- 2542** Schmidt, J. **Die Beeinflussung einer bedingten motorischen Fluchtreaktion der Ratte durch Noradrenalin, Serotonin und Lysergsäurediäthylamid.** (The susceptibility of the conditioned motor escape reaction in rats to noradrenaline, serotonin, and lysergic acid diethylamide.) *Acta Biologica et Medica Germanica*, 10:343-349, 1963.

The influence of noradrenaline, 5HT, and LSD, given i.p., s.c., or intracerebrally, on a conditioned escape reflex was determined in rats (100 to 200 g in weight). The rats were conditioned to jump onto a horizontal rod within 1 second after hearing a bell in order to avoid electric shock. The average of 10 reaction times was determined in groups of five rats before drug injection, and drug changes were compared with this baseline. With both peripheral and cerebral injection, all three drugs produced a dose-dependent

delay in reaction time. Only one-tenth to one-twentieth of the effective peripheral dose was required to produce equal effects with intracerebral injection. In contrast to noradrenaline and serotonin, i.p., or intracerebral LSD produced anxiety reactions in the rats.

Medical Academy
Magdeburg, Germany

- 2543** Tamura, Masaaki. The effects of some central nervous system depressants on conflict behavior in dogs. Japanese Journal of Pharmacology, 13:133-142, 1963.

A method is described for inducing conflict behavior, and the effects of drugs on this behavior are studied in 16 adult dogs (7 females and 9 males) weighing 6.5 to 15 kg. Having achieved the conditioned food-taking response, the dogs were further trained by punishment with an electric shock after completing 10 feeding cycles. This punishment procedure was applied every day after every 10 feeding cycles until conflict behavior developed. The abnormal behaviors consisted of one or two or no feeding cycles and an increase in the frequency of licking, smelling the cage or wandering, and lying or sitting. Phenobarbital (30 mg i.v.) produced a marked decrease in conflict behavior. Phenobarbital (20 to 60 mg/kg), pentobarbital (5 to 10 mg/kg), thiopental sodium (5 mg/kg), meprobamate (70 and 100 mg/kg), and ethanol (0.9 ml/kg) restored the inhibited food-taking response, but benactyzine (0.3 to 1.2 mg/kg) and chlorpromazine (0.5 to 1.5 mg/kg) had no restoring effect. Severe ataxia was produced by the barbiturates. Even with large doses of phenobarbital, the conditioned food-taking response was never abolished. Before producing conflict behavior, when large doses (1 mg/kg) of benactyzine or chlorpromazine (1 to 1.5 mg/kg) were given, the conditioned food-taking response was abolished.

Department of Pharmacology
University of Tokyo
Tokyo, Japan

- 2544** Hori, Y. & Yoshii, N. Cortical click-evoked potentials in the waking animal. Medical Journal of Osaka University, 13(4):395-412, 1963.

Cortical evoked potentials in the course of classical conditioning and changes in cortical evoked potentials during habituation or under the influence of drugs were studied in 12 adult dogs, which were not anesthetized and with chronically implanted electrodes. Three types of click-evoked potentials were distinguished—general, specific, and positive. An increase in amplitude and regularization of general type evoked potentials occurred with resulting widening of the area of their appearance under the application of novel stimuli or after the administration of caffeine natrio-benzoate (10 mg/kg). On the other hand, the same general type evoked potentials would decrease their amplitude, became irregular, and occur from a narrowed area of the cortex following habituation, establishment of the conditioned reflex, and extinction of the conditioned reflex. Chlorpromazine (5 mg/kg) and thiopental sodium (10 mg/kg) caused inhibitory evoked potential changes. Specific type evoked potentials were less likely to be altered than general type ones, but the general trend of changes was the same as in the general type. A discussion of various concepts relating to changes in cortical evoked potentials with possible mechanisms involved is presented.

Department of Physiology
Osaka University Medical School
Osaka, Japan

- 2545** Kugel, Robert B. & Alexander, Theron. The effect of a central nervous system stimulant (deanol) on behavior. Pediatrics, 31:651-655, 1963.

The effect of deanol (100 mg) on problem solving, and integrative and emotional behavior was studied in two groups of children—one with some form of cephalopathy (35) and those with behavior disorder only (7). The age range was from 6 to 13 years. The mean IQ was 78. Medical and psychological appraisals were made of the subjects at the inception of the study, at 3 months, and at the end (7 months). A crossover double-blind experimental design was used. There was no demonstrable influence of deanol over the placebo in bringing about

better scores on the psychological tests or upon behavior. No important side effects were noted.

Department of Pediatrics
State University of Iowa
Iowa City, Iowa

2546 Louisiana State University. **The effect of tranquilizing drugs on deviant responses and a deviant response scale.** Lindeman, Herman H., Adams, Henry E., & Humphries, Joanna, Baton Rouge, Louisiana, 1963, 9 p. Scientific report SP-1312, unclassified report.

A study was made to determine whether tranquilizing drugs have an effect on deviant responses and whether these drugs affected a scale developed on the Perceptual Reaction Test (PRT) for measuring schizophrenia (the SKI scale). One hundred seventy-two subjects were divided into four groups—43 female and 43 male schizophrenics in the no-drug group and 43 female and 43 male schizophrenics in the drug group. The majority of the drug patients were receiving chlorpromazine or trifluoperazine. Chlorpromazine dosage ranged from 25 to 100 mg q.i.d. Trifluoperazine dosage ranged from 5 to 150 mg q.i.d. Dosages of chlorpromazine and trifluoperazine combined were about 100 mg q.i.d. and 5 mg q.i.d., respectively. All drug subjects had been taking tranquilizers for at least 1 month prior to the study. The PRT, a test composed of 60 abstract designs drawn with a ruler and compass, was given to all subjects. There was no significant difference between drug and no-drug group on the SKI scale. When all of the options of the PRT were used, it was possible to discriminate between drug and no-drug groups.

Louisiana State University
Baton Rouge, Louisiana

2547 Institute for Behavioral Research. **Drug effects and complex behavioral repertoires under conditions of full environmental control.** Final report, Levison, P. K., Ferster, C. B., & Findley, J. D. Silver Spring, 31 October 1963, 17 p. Contract DA 18-108-AMC-26-A-CP3-4025, unclassified report.

This report describes a complex behavioral performance in which baboons "count" the number of objects presented to them visually. To date, one baboon has fully acquired the behavior, one counts to five

at a lower level of accuracy, and two baboons are in the early stages of training. The effects of an unknown CRDL drug injected i.m. (dosage not given) upon the performance of the fully trained animal were presented. Counting was severely disrupted, but the more difficult components of the sequence were considerably more sensitive to the compound. A drug-behavior interaction was proposed to account for a 4-day recovery period. Techniques for achieving and maintaining counting were described. Specific manipulations of experimental stimuli, responses, and positive and negative consequences of behavior were elaborated. Graphs, cumulative records of behavior, and photographs are included.

Institute for Behavioral Research
Silver Spring, Maryland

2548 Mulero, Ricardo. **The effects of Valium on psychological testing.** Nebraska State Medical Journal, 48:499-505, 1963.

Ten patients (24 to 62 years of age) with psychomotor depression were given 10 mg t.i.d. of diazepam for 5 to 7 days to determine the effects of the drug on psychomotor depression. Ten nursing students (20 to 22 years of age) were used as controls. Changes as a result of the drug were indicated by psychological testing before and after drug administration. The tests used included the Wechsler—Bellevue Intelligence Scale Form I (WB I), the Wechsler Adult Intelligence Scale (WAIS), the Bender—Gestalt test, and the Etch-a-Sketch test. The controls were given the same tests as the patients but received no medication. In the patient group, there were statistically significant increases in the second testing in the verbal IQ and the picture arrangement subtest of the WAIS—WB I combination. A significant increase was noted only in the picture arrangement subtest of the control group. These increases were interpreted as learning consequent to the test—retest process. No significant changes were noted in the Bender—Gestalt test by either patients or controls. There was a significant increase in the retest score of the Etch-a-Sketch test following drug administration to the patients. Since the controls did not show any significant increase, the improvement in visual motor control (as measured by this

test) in the patients would seem to be a result of the drug's action against anxiety, tension, and depression.

Creighton University
Omaha, Nebraska

2549 Hoerner, Earl F., Hansen, Harold T.,
Finley, F. Ray, & Howard, I. Ray.
**The effect of a skeletal muscle relaxant
on muscle extensibility.** *Industrial
Medicine and Surgery*, 32:516-520, 1963.

A test device for the assessing of a facet of the complex phenomena of muscle tone was tested. Use of the test to assess the effect of treatment on conditions of abnormally increased muscle tone and other applications is presented. The effect of Orpitol (0.5 mg fluphenazine and 100 mg orphenadrine) was investigated in 24 patients with arthritis, 13 with back myositis, and 13 with upper motor neuron affections. All patients were given Orpitol (two tablets daily) and a matching placebo in alternate, cross-over sequence. The total of all cases tested showed a reduction in mean score during the Orpitol trial when compared to the mean. For the placebo trial, the mean score showed an increase. The results were quite positive for the arthritis group treated with Orpitol. There is evidence, though not statistically significant, that Orpitol is useful for the treatment of back myositis and upper motor neuron affections. Side reactions were rare. The data are sufficient to recommend the use of Orpitol to control or reduce spasticity and spasm.

Rehabilitation Service
New Jersey Orthopedic Hospital Unit
Hospital Center at Orange
Orange, New Jersey

2550 Knoll, M., Kugler, J., Höfer, O., &
Lawder, S. D. **Effects of chemical
stimulation of electrically-induced
phosphenes on their bandwidth, shape,
number and intensity.** *Confinia Neurologica*,
23:201-226, 1963.

In order to study the differences, if any, between electrically-stimulated and chemically-stimulated phosphenes, the process of simultaneous electrical and chemical stimulation was investigated.

A subject with two relatively stable (electrically excitable) phosphenes was chosen. The stability of these two control patterns had been checked several times over a 6-month period. The main subjects of observation were the shape, bandwidth, number, and intensity of patterns. Both EEG and ECG recordings were obtained. The drugs used were mescaline (220 mg), psilocybin (6 mg), and LSD (three injections: 0.01, 0.01, and 0.02 mg). During electrical and maximum chemical stimulation, the new drug-induced pictures prevail, and the control patterns disappear except with LSD. Electrical stimulation increased the brightness and changed the shape of drug-induced phosphenes even during maximum chemical stimulation. The transition from one particular picture to another was slower with psilocybin than with the other two drugs. The electrically-stimulated phosphenes consisted of patterns and movements of white light against a black background, whereas the chemically-stimulated phosphenes were colorful, with mescaline producing the brightest pictures. As a result of chemical excitation, there is a temporary increase of the original two control patterns in intensity and bandwidth from about 13% up to 100%. The "glorification" effect of external objects was noted only with mescaline. Depth perception varied with the stimulant. Concepts of the neurophysiological mechanisms producing the phosphene patterns are discussed.

Institute for Electronic Technology
Technical University
Munich, Germany

2551 Mancini, E. & Lecce, C. **Le
esperienze deliranti e allucinatorie
di presenza animale.** (A proposito di un
caso osservato nel corso di terapia con
psicofarmaci.) The delusional and hallucinatory experience of the presence of animals. (A propos of a case observed in the course of treatment with psychopharmacologic drugs.) *Ospedale Psichiatrico*,
31:197-210, 1963.

The occurrence of hallucinations is reported in a 45-year-old male depressive patient being treated with levopromazine. The patient had not shown hallucinations as part of his symptomatology prior to drug therapy. He had received insulin shock therapy over a period of 3 months, and when this proved unsuccessful, imipramine therapy was initiated. The

patient was refractory to imipramine, and levopromazine therapy was begun. On the fourth day of levopromazine treatment, and for 2 weeks following, the patient experienced hallucinations at twilight and during the night. Other examples of hallucinatory attacks precipitated by imipramine followed by promazine therapy, as reported in the literature, are presented.

Provincial Neuropsychiatric Hospital
Ancona, Italy

See also: 2426, 2427, 2438

PHARMACOLOGY

- 2552 Gorin, Manuel H. The biochemistry of the psychotic state. *Journal of Asthma Research*, 1(2):151-156, 1963.

The present status of the theory that schizophrenia has a chemical cause has been evaluated, and it was concluded that no evidence as to the nature of the chemical aberration has been uncovered. Psychotoxic substances belonging to the LSD-25 family produced by emotional stress and circulated by the blood to the brain are not considered the chemical causes of schizophrenia, due to the tolerance mechanism of the LSD family that should moderate their toxic action. This reviewer considers the tolerance factor as a clue of great promise because in the tolerance mechanism are means for terminating the action of psychotoxins as well as means for controlling the effect of future release of toxins into the brain.

220 9th Street
San Francisco 3, California

- 2553 Yeh, Eng-Kung. A study of the effects of Niamid on autonomic nervous system of normal human subjects. *Journal of the Formosan Medical Association*, 62(2):122-129, 1963.

A study was conducted to determine the effect of nialamide on the autonomic nervous system in 12 healthy, male, medical students, ranging in age from 23 to 25 years and in weight from 55 to 63 kg. The students were divided into two equal groups of six subjects each. The control group received one tablet of placebo t.i.d. for 10 days, and the other group was given a metacholine chloride injection of 10 mg i.m., an adrenaline injection of 0.01 mg/kg i.m., and nialamide medication of 25 mg t.i.d. for 10 days. The nialamide and placebo were administered in a double-blind manner. Test results showed no significant change in the autonomic balance and responses of the autonomic nervous system to methacholine chloride injection after nialamide medication. Although not statistically significant, the systolic blood pressure rose more after an adrenaline injection for nialamide as compared with the control group.

No side effects were observed during nialamide administration. One patient showed an increase in appetite and in general well-being.

Department of Neurology and Psychiatry
National Taiwan University Hospital
Taiwan, Formosa

- 2554 U.S. Army. Investigation of Indoklon as a convulsive agent in the treatment of psychiatric disorders. Annual Progress Report. Kleinmann, Mortimer V., Jr. & Cordes, Charles K. San Francisco, California, Research and Development Service, Letterman General Hospital, 1963, p. 45-48.

A study to investigate the suggested advantages of hexafluorodiethyl ether (Indoklon) over ECT as a convulsant agent was carried out in the treatment of eight patients with psychiatric disorders. The patients received a total of 53 treatments with the drug. The drug's efficacy was evaluated on the basis of patient acceptance, simplicity of procedure, incidence of compression fractures of the thoracic spine, incidence of cardiopulmonary complications, and the degree of confusion and disorientation following treatment. The patient's acceptance of the Indoklon was far greater than of ECT. Succinyl choline, a muscle relaxant, may be used without pentothal if administered 5 seconds after Indoklon. If it is given before Indoklon, some patients' experience a suffocation feeling. The degree of confusion and disorientation following treatment, without the use of pentothal, is markedly reduced. No compression fractures of the thoracic spine have been observed. The administration of the drug is simple and it appears feasible to administer it with no anesthetic agent or muscle relaxant.

Letterman General Hospital
San Francisco, California

2555 Rupkey, A. Katherine, Gold, Ruth, Rugh, Roberts, & Wang, S. C.
Effects of drugs alone, or combined with refrigeration, in protecting female mice against X-irradiation-induced sterility. Radiation Research, 19:88-103, 1963.

Virgin CF-1 female mice, 10 to 12 weeks old (25 to 30 g in weight), were used to study the effect of i.p. injections of Hydergin (0.3 and 0.6 mg/kg), chlorpromazine (23 and 45 mg/kg), promethazine (23 and 45 mg/kg), urethan (0.6 gm/kg), reserpine (3.3 mg/kg), and lytic cocktails (Hydergin--chlorpromazine, Hydergin--promethazine, and chlorpromazine--promethazine) in protecting against sterility induced by whole-body irradiation at dose levels of 25, 50, 100, and 150 r. The controls received physiological saline. One-half of the drug-pretreated groups were cooled in a refrigerator freezer to 20° to 23° C rectal temperature. When the animals' temperatures reached the desired level, all 20 animals in each group were exposed to irradiation. After 5 weeks, a male was placed in each cage for a 40-week period. Percentage of fertility and average litter size were calculated for each 10 consecutive 4-week period. Fertility of the normal animals ranged from 69% to 89% through the eighth 4-week period and dropped to 39% by the tenth 4-week period. The average litter size ranged from 6.7 to 10.1 over the first 7 periods and dropped to 4.6 by the 10 period. Average number of litters (ANL) over the first 20 weeks and the second 20 weeks was significantly lower for the noncooled mice than for the normals in those receiving 25 r of irradiation. The ANL for both periods was higher for the chlorpromazine-treated animals in this group. All types of drug pretreatment, chlorpromazine and reserpine, clearly showed the most consistent radioprotective effect on fertility, especially at the level of 50 r and 100 r of irradiation. All control mice receiving 150 r were sterile through the period of observation. A 10% fertility was observed with reserpine or chlorpromazine, with or without cooling, and a 10% to 15% fertility with cooling, Hydergin--chlorpromazine or chlorpromazine--promethazine. Refrigeration appears to afford additional radioprotection.

College of Physicians and Surgeons
Columbia University
New York, New York

2556 Poulson, Evelyn & Robson, J. M.
The effect of amine oxidase inhibitors on pregnancy. Journal of Endocrinology, 27:147-152, 1963.

The effects of seven amine oxidase inhibitors on pregnancy were investigated in white mice of known fertility. The drugs were administered over days 1 to 3, 1 to 6, 4 to 7, 6 to 11, and 11 to 16 of pregnancy in various groups of mice. The following drugs were given in a daily single s.c. injection: iproniazid (5 or 10 mg/day); 2,2'-(*p*-phenylenedioxy)-di-(ethylhydrazinium) chloride (HP 1325) (2 or 5 mg/day); nialamide (4 mg/day); heptylhydrazine (0.5 mg/day); harmaline HCl (0.4 or 0.8 mg/day); tranlycypromine sulfate (0.1 or 0.2 mg/day); MO-911, *N*-benzyl-*N*-methyl-2-propynylamine hydrochloride (MO-911) (2 mg/day); and isoniazid (3 mg/day). Four of the compounds were derivatives of hydrazine, and three were not. All four derivatives of hydrazine and HP 1325 produced toxic effects in early pregnancy but were relatively inactive later; harmaline and tranlycypromine had no effect. The effect of HP 1325 was, to a great extent, reversed by either progesterone or prolactin, suggesting an interference with the hormonal mechanism responsible for the maintenance of pregnancy. The HP 1325 (and 5HT) did not interrupt pseudopregnancy, indicating that luteal function is not completely inhibited. Evidence is adduced that the effects on pregnancy are not related to any particular chemical structure or to the amine-oxidase activity of the compound tested.

Guy's Hospital Medical School
London, S.E.1, England

2557 Abood, L. G., Kimizuka, H., Rogeness, G., & Biel, J. H. Some antidepressant drugs and their mechanism of action on excitable membranes. Annals of the New York Academy of Sciences, 107: 1139-1146, 1963.

The effect of PMCG on the intracellular resting potential of the frog sartorius muscle fibers was studied in a ringer and a Ca-free solution. With addition of PMCG or norimipramine, the decline in the resting potential and twitching, which occurred upon transferring muscles from ringer to a Ca-free solution, were prevented. However, it was possible to restore it by the addition of 10^{-4} PMCG or norimipramine when the resting potential had dropped 50% in the

Ca-free medium. In order to further test the hypothesis that Ca^{2+} and PMCG were acting similarly upon membranes, a comparison was made of their actions upon properties of interfacial films comprised of various lipids and proteolipid complexes. At a concentration of 0.1 mM Ca^{2+} , the lecithin (surface concentration 24 mg/m^2) film was virtually saturated with Ca^{2+} in the absence of other cations. Consequently, the decrease in the adsorption of Ca^{2+} with increasing concentration of PMCG would indicate replacement of Ca^{2+} by the agent. With increasing concentration of PMCG, the adsorption of Ca^{2+} to the proteolipid film decreases. At pH 2, 0.1 mM Ca^{2+} had no effect on the surface pressure, surface viscosity, and the limiting area, whereas at pH 7.6, the film showed increased viscosities. At pH 7.8, all three agents produced marked increase in surface viscosity.

Department of Psychiatry and Biochemistry
University of Illinois
College of Medicine
Chicago, Illinois

2558 Plummer, Albert J. & Furness, Patricia A. **Biological estimation of the intensity and duration of action of monoamine oxidase inhibitors.** *Annals of the New York Academy of Sciences*, 107:865-877, 1963.

A pharmacological method is described for the detection and estimation of the activity of centrally acting MAO inhibitors. This method is based on the principle of the reversal of the sedative effect of reserpine to stimulation when an MAO inhibitor is administered prior to reserpine. Experiments were performed in which graded doses of several MAO inhibitors were administered s.c. to mice. After a period of 4 hours, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, or 20 mg/kg of methyl-O-(tetrahydro-2-pyranyl) reserpate (SU-7064) was injected s.c. This compound was used in preference to reserpine due to its rapid onset and relatively brief duration of the stimulation that provides a more uniform and reproducible measure of effect than does reserpine. In the case of 2-hydrazino-tetrahydronaphthylene (SU-8403), a dosage schedule of 5, 10, 20, and 40 mg/kg was selected. The SU-8403 was characterized by a rapidly developing and marked MAO inhibitory activity, which could be observed for as long as 6 days. With phenylisopropyl hydrazine (JB-516), the same dosage schedule was used (5 to 10 mg/kg), and the 20 mg/kg dose was equivalent to 40 mg/kg of SU-8403

as an MAO suppressant. The MAO inhibitory effect was noticeable immediately and lasted about 1 hour. A dosage ranging from 40 to 120 mg/kg, in 20 mg/kg ranges, was used in the study of *N*-benzyl-*N*-methyl-2-propynylamine hydrochloride (MO-911). The 120 mg/kg dose was found to be equivalent to 40 mg/kg of SU-8403. In the study of SKF-385-B (2.5 to 20 mg/kg), the 10 mg/kg dose was equivalent to 40 mg/kg of SU-8403. In the case of iproniazid (100 mg/kg), no comparison of potency could be made due to the gradual but steady increase in enzymatic inhibition. A biological method was described in which the MAO activity of the brain was determined by the rate of oxidation of the substrate, serotonin, which was incubated with the brain homogenate. Since there was a lack of parallelism between the results obtained by the two methods, it was suggested that concrete pharmacological observations should be relied upon for estimates of inhibitor activity.

CIBA Pharmaceutical Company
Summit, New Jersey

2559 Krivoy, William A., Lane, Montague, & Kroeger, Donald C. **The actions of certain polypeptides on synaptic transmission.** *Annals of the New York Academy of Sciences*, 104:312-329, 1963.

A report of investigations that concern various aspects of the physiological role of polypeptides and the pharmacological relationships that exist between polypeptides and psychochemicals is presented. In experiments with guinea-pig brain extract, it was found that substance P disappeared at a rapid rate when incubated with the brain extract and LSD-25 (10^{-8} , 10^{-9} , and 10^{-10} M) inhibited the disappearance. There seemed to be a rough correlation between the concentrations of LSD and the degree of inhibition. Bromlysergic acid inhibited the action of LSD so that the disappearance of substance P proceeded at its normal rate. When the influence of various other drugs on the rate of disappearance of substance P was compared, it was found that none of the drugs possessed any influence. Chlorpromazine (10^{-7} M) reduced the rate of disappearance of bradykinin (10^{-7} M) incubated with brain extracts. In decerebrate and decerebrate-spinal cats administered submaximal stimuli (2.5 cycles/second), LSD (10 µg/kg) alone and in combination with substance P (12 units/kg) produced augmentation of dorsal root potential IV. Bromlysergic acid (100 µg/kg) had no effect on the dorsal

root preparation, but blocked the action of LSD. Chlorpromazine (1.0 to 2.5 mg/kg) alone or in combination with bradykinin (0.3 µg/kg) produced inhibition of dorsal root potential V in decerebrate and decerebrate-spinal cats subjected to maximal stimuli (0.5 cycles/second). The β-melanocyte stimulating hormone (β-MSH) in doses of 100 µg/kg produced enhancement of dorsal root potential V and at 100 µg/kg to 200 µg/kg produced augmentation of dorsal root potential V, which had been inhibited by chlorpromazine. The β-MSH (0.25 µg/kg) resulted in enhancement of monosynaptic reflex potentials. The α-melanocyte stimulating hormone, adrenocorticotrophic hormone, oxytocin, and vasopressin had no action on monosynaptic reflex potentials. Reserpine (5 mg/kg) had no effect on dorsal root potentials and did not modify the action of bradykinin. Dibenzylamine (0.5 mg/kg) and morphine depressed dorsal root potential V. In order to study the behavioral effects, the amplitude variations (AV) of the Gymnotidae eigenmannia were observed. The LSD (5×10^{-5} µg/ml) produced a decrease in AV, and substance P (0.001 units/ml), given after LSD, produced a further decrease. The β-MSH (0.5 µg/ml) produced a decrease in AV that was not seen with α-MSH (0.2 µg/ml). These data indicate a physiological role of substance P (augments hyperexcitability), of bradykinin (depresses hyperexcitability), and of β-MSH (augments hyperexcitability, more potent than substance P) on the nervous system.

Baylor University
College of Medicine
Houston, Texas

2560 Goldstein, Leonide, Murphree, Henry B., & Pfeiffer, Carl C.
Quantitative electroencephalography in man as a measure of CNS stimulation.
Annals of the New York Academy of Sciences, 107:1045-1056, 1963.

The technique of quantitative electroencephalography was used to determine the effect of stimulant drugs on the mean energy content (MEC) of the EEG in normal adult volunteers (21 to 24 years of age). The following drugs were tested: 0.7 mg/kg pentobarbital; 250 mg caffeine; 0.2 mg/kg α-amphetamine; 0.3 µg and 1.0 µg LSD-25; 3 and 15 mg/kg deanol; 50 and 120 mg 2-methyl-3-piperidinopyrazine (W 3207 B); and 20 mg tranlycypromine. All drugs and placebo were given orally after a 10 to 15 minute control recording. After the drug was

given, two to six samples of the energy content of the left occipital EEG were obtained (each was 10 minutes in duration) at 30, 60, 90, 120, 150, and 180 minutes. In some cases, the EEG was recorded at 360 and 420 minutes. Quantitative analyses of integrated EEG records showed that the electrical activity of the brain is organized, but highly variable. With stimulants, such as amphetamine, caffeine, LSD-25, and deanol, the MEC of the EEG decreased. With the exception of deanol, this effect was accompanied by a reduction in EEG variability. Single doses of the MAO inhibitors exerted no detectable effect up to 6 hours after drug administration. Possible interpretations of the mode of action of stimulants are discussed.

New Jersey Neuropsychiatric Institute
Princeton, New Jersey

2561 Zeller, E. Albert. **A new approach to the analysis of the interaction between monoamine oxidase and its substrates and inhibitors.** Annals of the New York Academy of Sciences, 107:811-821, 1963.

The formation of the MAO--substrate complex is discussed in terms of chemical configuration, and the findings are extended to include the actions of various MAO inhibitors. Beef-liver or rabbit-liver MAO was used in all experiments. When ortho-, meta-, and para-substituted benzylamines were tested as substrates, it was found that meta-substituted compounds were superior substrates, regardless of the group introduced into the aromatic ring. The concept of the formation of eutopic and dystopic complexes between substrate and MAO is described, and mathematical relationships are derived for determining the kinetics of substrate concentration and reaction rate. Two-dimensional models for eutopic and dystopic complexes are given. The concepts derived in the MAO--substrate experiments suggested that: (1) The MAO inhibitors may attach to MAO in more than one way, analogous to eutopic and dystopic complexes. (2) The relative degree of eutopic and dystopic orientation of the substrate could influence the interaction between MAO and some MAO inhibitors. Results of MAO inhibition by methoxy derivatives of phenylisopropylhydrazine, tranlycypromine, o-iodobenzylamine, and pargyline in the presence of various substrates are presented.

Department of Biochemistry
Northwestern University Medical School
Chicago, Illinois

2562 Goldstein, M. & Musacchio, J. M.
Effects of monoamine oxidase inhibition on biogenic amine metabolism. *Annals of the New York Academy of Sciences*, 107: 841-847, 1963.

An evaluation and comparison of the metabolism of administered dopamine and norepinephrine in normal and MAO inhibited rats were made. The cerebral metabolism of administered DOPA-C¹⁴ in untreated animals and in animals treated with specific inhibitors of MAO and CMT (catechol methyl transferase) is discussed. A comparison of the amount of excreted deaminated metabolites of dopamine-1-C¹⁴ and norepinephrine-7-H³ in normal and iproniazid (100 mg/kg i.p.) pretreated white rats showed that dopamine is deaminated by MAO to a much greater extent than is norepinephrine, and the inhibition of MAO alters to a much greater extent the metabolism of dopamine than that of norepinephrine. In studies of the total radioactivity of N-acetylated phenolic metabolites derived from dopamine and norepinephrine in normal and iproniazid-treated animals, the results show that dopamine undergoes N-acetylation to a greater extent than does norepinephrine. The MAO inhibition increases the inactivation of dopamine and norepinephrine by N-acetylation. Inhibition of MAO enhanced the inactivation of the catecholamines by N-acetylation, and this pathway is more significant for the metabolism of dopamine than that of norepinephrine. To determine which enzyme, MAO or CMT, has a greater effect on the metabolism and synthesis of dopamine and norepinephrine in the CNS, the metabolism of DOPA-C¹⁴ was investigated in untreated animals and in animals treated separately and simultaneously with MAO (iproniazid 100 mg/kg i.p.) and CMT (tropolone 40 mg/kg i.p.) inhibitors. In iproniazid-treated animals, the levels of DOPA-C¹⁴ are higher than in untreated or tropolone-treated animals. The MAO inhibition decreased the concentration of deaminated metabolites in the brain. Iproniazid increased the concentrations of catecholamines and methoxyamines. Tropolone treatment caused only a slight increase in the catecholamine concentration. The highest increase in catecholamine levels was obtained with combined treatment of iproniazid plus tropolone. The highest concentration of dopamine-C¹⁴ and 3-methoxy-dopamine-C¹⁴ was observed after simultaneous treatment with tropolone and iproniazid. Iproniazid had a potentiating effect on dopamine-C¹⁴, 3-methoxy-dopamine-C¹⁴, and norepinephrine C¹⁴. In iproniazid-treated animals, dopamine is

inactivated to a greater extent by CMT than is norepinephrine, and this inactivation is inhibited by tropolone.

New York University
College of Medicine
New York, New York

2563 Pscheidt, Gordon R. Anomalous actions of monoamine oxidase inhibitors. *Annals of the New York Academy of Sciences*, 107:1057-1067, 1963.

In an attempt to explain the various actions and interactions of MAO inhibitors, several short studies are presented as illustrations. The effects of tranlylcypromine, pheniprazine, and iproniazid on the rabbit EEG, and comparison of the results with the brain amine levels of norepinephrine and serotonin showed that MAO inhibitors differed considerably in their action. Both pheniprazine and tranlylcypromine rapidly elevated the serotonin and norepinephrine levels, whereas iproniazid induced a gradual rise. Pheniprazine and tranlylcypromine produced alerting of the EEG, but iproniazid did not produce any desynchronization with doses up to 400 mg/kg. Etryptamine (2 mg/kg intracarotid injections) produced alerting in rabbits, and 2 to 15 mg/kg i.v. caused delayed arousal. Etryptamine (5 mg/kg) had little effect on the serotonin or norepinephrine levels in the brain. No stereospecificity was noted; the dextro, levo, and racemic forms of etryptamine were equally active. The cat, dog, and frog exhibit anomalous responses to administration of MAO inhibitors. The interaction of MAO inhibitors with reserpine is another area in which anomalous actions of certain inhibitors may be observed. Nialamide (25 mg/kg) combined with 1 mg/kg of reserpine produced serotonin levels in excess of that produced by the nialamide alone. A study is reported in which the antagonism of isocarboxazid (30 mg/kg/day) to the reserpine-induced (4 mg/kg/day) changes in urine volume and mineral excretion demonstrates that MAO inhibitors may elicit physiological or biochemical responses, which become apparent only when the organism is pretreated with another drug

Thudichum Psychiatric Research Laboratory
Galesburg State Research Hospital
Galesburg, Illinois

- 2564 Horita, A. Some antagonists of the monoamine oxidase inhibitors. *Annals of the New York Academy of Sciences*, 107:951-957, 1963.

Studies demonstrating that antagonism of the hydrazine-type inhibitors of MAO may be accomplished by their interaction with a number of biological substances are described. Pheniprazine 10^{-5} M completely blocks the MAO activity in the liver homogenate; Na pyruvate had no influence on the MAO, but antagonized the pheniprazine so that less than half of the original inhibition was present. However, if the pyruvate was added after the inhibitor, no antagonism occurred. It was found that compounds possessing the $-NHNH-$ or $-NHNH_2$ structures were antagonized by Na pyruvate (0.1 M). In intact rats, after 500 mg/kg of Na pyruvate, pheniprazine (1 mg/kg) exerted only 20% inhibition. Both brain and liver were influenced in the same manner. However, pyruvate was incapable of antagonizing the iproniazid block of MAO. The results indicate that, in the case of pheniprazine, a chemical interaction between the hydrazine moiety and the carbonyl group of Na pyruvate is taking place and results in the formation of a nonactive compound. Absorption spectra of solutions of Na pyruvate, pheniprazine, and a mixture of the two lends credence to this hypothesis. Comparative studies of the MAO inhibiting property of iproniazid and pheniprazine in vitro in the presence of red blood cells are described. The mechanism of the influence of red cells on either iproniazid or pheniprazide does not appear to be identical to the antagonism exerted by the carbonyl-containing agents. In order to study the influence of tissue components on the MAO blocking actions of the hydrazine-type inhibitors, iproniazid and pheniprazine were incubated with liver and brain homogenates. No loss of inhibitor activity in the supernatant (up to 90 minutes) compared with incubation in buffer solution was observed with iproniazid. Pheniprazine was inactivated or taken up by both liver and brain homogenates, and the supernatant showed significant loss of pheniprazine activity within 10 minutes. A similar picture was observed in the intact animals.

Department of Pharmacology
University of Washington
School of Medicine
Seattle, Washington

- 2565 Arora, R. B. Mechanism of action of monoamine oxidase inhibitors in experimental myocardial infarction in the pig. *Annals of the New York Academy of Sciences*, 107:1152-1158, 1963.

Various MAO inhibitors (hydrazine and nonhydrazine derivatives) were tested for their beneficial effects on domestic pigs of both sexes (3 to 4 months of age, 15 to 25 kg body weight) in which myocardial infarction had been produced by two-stage coronary ligation. The coronary ligation was performed after 4 days of pretreatment with the respective MAO inhibitor. The effects of the drugs were expressed as percentages of the inhibition of the MAO activity ($25\mu\text{l/g/hour}$ to $30\mu\text{l/g/hour}$) in normal pigs. All of the drugs were given i.m. at a dose of 20 mg/kg/day. Of the drugs tested (isonicotinic acid hydrazine, *N'*-isonicotinyl-*N''*-isopropylhydrazine, *N'*-palmitoyl-*N''*-isopropylhydrazine, L-glutamic acid- α -isopropylhydrazine nialamide, and *N*-benzyl-*N*-methyl-2-propynylamine HCl), only L-glutamic acid- α -isopropylhydrazine showed evidence of improvement in myocardial infarction. In all the nialamide-treated animals, there was no evidence of interarterial coronary anastomosis. It was concluded that MAO inhibition was probably the most important factor that determined the ultimate beneficial effect.

All-India Institute of Medical Sciences
New Delhi, India

- 2566 Walaszek, E. J., Huggins, C. G., & Smith, C. M. Drugs that modify actions of pharmacologically active polypeptides. *Annals of the New York Academy of Sciences*, 104:281-289, 1963.

A number of drugs were studied for their possible interaction with pharmacologically active polypeptides on various biological test systems. Morphine (10^{-7} , 10^{-6} , and 10^{-5} M), phenoxybenzamine (10^{-7} M), and a combination of the two drugs were found to inhibit the contractile responses to angiotensin ($0.004\mu\text{g/ml}$) and substance A ($2\mu\text{g/ml}$) of the guinea-pig ileum. Harmaline (1.6×10^{-6} M, 3.2×10^{-6} M, and 6.6×10^{-6} M) and ibogaine (1.3×10^{-7} M, 4.0×10^{-7} M, 8.0×10^{-7} M, and 1.6×10^{-6} M) antagonized responses to substance P (0.3 or 0.4 U/ml), angiotensin, and substance A ($2\mu\text{g/ml}$). Responses to bradykinin were not affected by these agents. Bulbocapnine (60 mg/kg) potentiated the cardiovascular response of vasopressin (0.5 unit) in the dog and at a

dose of 4 μ g/ml potentiated the contractile effect of oxytocin (0.002 units/ml and 0.001 units/ml) on the isolated rat uterus. Dichloroisoproterenol (10 mg/kg) produced an antagonism toward the cardiovascular responses to oxytocin (0.01 units/kg) of chicken blood pressure.

Kansas University Medical Center
Kansas City, Kansas

- 2567** Spector, Sydney. **Monoamine oxidase in control of brain serotonin and norepinephrine content.** *Annals of the New York Academy of Sciences*, 107:856-864, 1963.

The nonhydrazide MAO inhibitor, MO 911, was studied in order to detect the effect of MAO inhibition on brain norepinephrine (NE) and 5HT. Within 1 hour after the injection of MO 911 (25 mg/kg i.v.) into rabbits, MAO was almost completely inhibited, NE was increased about 50%, and 5HT was increased about 200%. The MO 911 (25 mg/kg) was given to rabbits daily. In 4 days, NE was increased twofold and 5HT was elevated to 5 times its normal value. When the drug was withdrawn, the effects (mydriasis, spontaneous motor activity, and resistance to handling) disappeared within 3 days, the NE level declined, but the 5HT level was still elevated. The NE content of the superior cervical ganglia was elevated almost threefold in rabbits given MO 911 (10 mg/kg i.v.) daily for 7 days. The MO 911 (10 mg/kg i.v.) given to cats for 14 days had no effect on the ganglionic level of NE. The daily administration of MO 911 to cats (75 mg/kg i.p.) for 9 days and to dogs (10 mg/kg p.o.) for 25 days produced an elevation of brain 5HT without affecting that of NE. Rabbits given MO 911 (50 mg/kg i.v.) 3 hours after reserpine (5 mg/kg i.v.) showed elevated levels of 5HT and dopamine but remained sedated for 10 to 12 hours, at which time the NE level was increased. These results suggest that MAO has the intracellular role of regulating the NE and 5HT content of storage compartments and that free NE is very active in antagonizing reserpine effects.

National Heart Institute
National Institutes of Health
Bethesda, Maryland

- 2568** Gey, K. F., Pletscher, A., & Burkard, W. **Effect of inhibitors of monoamine oxidase on various enzymes and on the storage of monoamines.** *Annals of the New York Academy of Sciences*, 107:1147-1151, 1963.

The effects of various hydrazine and nonhydrazine MAO inhibitors on the activity of diamine oxidase (DAO), of aromatic amino acid decarboxylase (DCA), and of choline dehydrogenase (CDH) were compared in vivo. The dose of various MAO inhibitors necessary for 50% inhibition of MAO in rat brain (ED_{50}) was plotted against the dose for 100% increase in 5HT ED_{100} to determine the relation between MAO inhibition and amine accumulation. Results showed that inhibition of DAO, DCA, and CDH had little relation to the clinical efficiency of MAO inhibitors. The ED_{100} for tranylcypromine, pheniprazine, nialamide, and pivazid for amine accumulation was about 5 to 8 times higher than the ED_{50} for MAO inhibition, but isopropylhydrazine, isocarboxazid, iproniazid, and benzylhydrazine had an ED_{100} for amine accumulation that was about 12 to 30 times higher than the ED_{50} for MAO inhibition. It was concluded that the accumulation of brain monoamines is in part related to another mechanism, besides MAO inhibition, that either diminishes or enhances the increase of amines.

F. Hoffman-La Roche Company Limited
Basel, Switzerland

- 2569** Everett, G. M., Wiegand, R. G., & Rinaldi, F. U. **Pharmacologic studies of some nonhydrazine MAO inhibitors.** *Annals of the New York Academy of Sciences*, 107:1068-1080, 1963.

The pharmacology of representative members of two series of nonhydrazine MAO inhibitors pargyline and MO 1255, has been reviewed. Pargyline had the properties of a nonreversible MAO inhibitor both in vitro and in vivo. It proved to be an effective antidepressant and antihypertensive drug, and its low toxicity in animals was also found in man. The MO 1255 was not active in vitro but was highly effective in vivo. Its duration of action (3 days) was relatively short as compared to the long-lasting effects (8 days) of pargyline and hydrazine MAO inhibitors. With MO 1255 (400 mg/day in man), no antihypertensive effects or fall in blood pressure occurred, whereas antidepressant effects and increased motor activity were observed at doses of 100 mg/day. The antidepressant effects and

increased motor activity may be due to the increase of biogenic amines after these MAO inhibitors. The MAO inhibitors, with their long duration of action, are potential mobilizing agents in man, especially if a nontoxic drug of this type is discovered.

Abbott Laboratories
Chicago, Illinois

- 2570** Saarimaa, H. A., Sourander, Chr., & Rinne, U. K. **The effect of chlorpromazine on the secretion of corticotrophin in psychiatric patients examined by the Metopiron test.** *Acta Psychiatrica Scandinavica*, Supplement 169:362-364, 1963.

The Metopiron (SU 4885, a synthetic compound that inhibits selectively the enzymatic 11 β -hydroxylation in the steroid ring, thereby inhibiting the biosynthesis of hydrocortisone, corticosterone, and aldosterone) test was used to study the effect of chlorpromazine on ACTH secretion in 10 patients with paranoid schizophrenia. There were five men and five women, 36 to 71 years of age (mean age 51.3 years). No medication was given 6 months prior to the test. The test lasted 3 days; the first and third days were the control days; on the second day, 750 mg of Metopiron p.o. were given, and 24-hour urine was collected. Excretion of 17-hydrocorticosteroids was determined. After this test, patients were given 300 mg/day chlorpromazine in tablet form for 14 days, and then a new 3-day test was performed. Metopiron caused a statistically significant increase in the excretion of 17-hydroxycorticosteroids before therapy, but not after chlorpromazine medication. There was a significant increase in diuresis.

Kupittaa Hospital
Turku, Finland

- 2571** Ganrot, P. O., Gottfries, C. G., & Rosengren, E. **Effects of some psychotropic drugs on the metabolism of catecholamines and 5-hydroxytryptamine in human brain.** *Acta Psychiatrica Scandinavica*, Supplement 169:248-252, 1963.

Studies of the effects of iproniazid (75 to 125 mg/day), reserpine (0.5 to 2 mg/day), imipramine, and amitriptyline on the metabolism of catecholamines and 5HT, and on MAO activity in the brain and liver were carried out in patients who had died from

cancer or circulatory diseases. The control patients had received no drugs that were known to influence metabolism of amines. The concentration of dopamine, noradrenaline, and 5HT decreased slowly 3 days after death, and the MAO activity did not vary to any appreciable extent during this period. Iproniazid was found to inhibit MAO activity in the brain and the liver by more than 95%. The recovery of monoamine oxidase was studied in five patients who had been dropped from iproniazid treatment 8 weeks previously. The recovery of monoamine oxidase was fairly slow in the brain but appeared to be more rapid in the liver. The concentrations of dopamine, noradrenaline, and 5HT were substantially higher in the iproniazid-treated group than in the control group. Noradrenaline and 5HT concentrations were lower in the reserpine-treated patients than in the controls. Reserpine only had a moderate effect on the dopamine level. No changes in MAO activity or monoamine concentration were noted after imipramine or amitriptyline.

Department of Pharmacology
University of Göteborg
Göteborg, Sweden

- 2572** Schou, Mogens. **Electrocardiographic changes during treatment with lithium and with drugs of the imipramine-type.** *Acta Psychiatrica Scandinavica*, Supplement 169:258-259, 1963.

The ECG changes in one-fifth of 12 male patients treated with lithium, with amitriptyline, and with N 7001 (related to amitriptyline) consisted of inversion of T₁ and T₂, flattening, or isoelectricity. Treatment with G 35020 and N 7049, the desmethyl derivatives of imipramine and N 7001, respectively, did not produce ECG changes. Only the T-waves of the ECG were affected, and the changes were not related to sex or to age. No change in the ECG was noted in 22 patients with ECG abnormalities before treatment with lithium and imipramine thymoleptics. These results indicate that the T-wave changes are harmless phenomena.

Clinical Chemistry Laboratory
State Mental Hospital
Risskov, Denmark

- 2573** Moran, Neil C. & Westerholm, Barbro.
The influence of reserpine on
5-hydroxytryptamine and histamine content
of rat mast cells and some rat tissues.
Acta Physiologica Scandinavica, 58:20-29,
1963.

The effect of reserpine on mast cells in rat peritoneal was determined in vitro, and the effect of reserpine on the 5HT and histamine content of certain rat tissues was determined in vivo and compared to the effect of compound 48/80. Male albino, Wistar rats (200 to 400 g in weight) were used in all of the experiments. Rat peritoneal mast cells were incubated at 37° C with reserpine or compound 48/80, and intestine was incubated at 37° C with various concentration of reserpine; the 5HT and histamine content of the medium was determined. Peritoneal mast cells and pieces of abdominal skin, ileum, duodenum, pylorus, fundus, and brain from rats treated with a single dose of 5 mg/kg reserpine or five doses of compound 48/80, beginning with 100µg and increasing by 100µg/day up to 500µg, were also assayed for 5HT and histamine. Reserpine did not release 5HT or histamine from rat mast cells in vitro. In vivo, reserpine caused a moderate reduction of the number of mast cells in the peritoneal fluid and of the cellular 5HT content. Reserpinized rats showed a reduction of 5HT in the brain, but not in the skin, ileum, duodenum, pylorus, or fundus. Histamine was reduced to 35% of control value in vivo, but no decrease occurred in vitro. Treatment with compound 48/80 caused a disappearance of all mast cells and of 5HT and histamine from the peritoneal fluid. Reserpine depleted histamine from the intestine, which is not of mast cell origin.

Emory University
Atlanta, Georgia

- 2574** Johnson, G. E. The effect of cold exposure on the catecholamine excretion of adrenalectomized rats treated with reserpine. *Acta Physiologica Scandinavica*, 59:438-444, 1963.

Experiments were designed to determine the effect of reserpine on the synthesis of noradrenaline in adrenergic nerves in vivo, based on the assumption that if reserpine does inhibit synthesis, then a reserpinized, adrenalectomized rat subjected to cold stress should show no increase in noradrenaline excretion. Male Sprague-Dawley rats (175 to 250 g in weight) were bilaterally adrenalectomized and divided into two groups, one

treated with 0.25 mg/kg reserpine daily and the other serving as control. Both groups of rats were given cortisone and desoxycorticosterone daily. Four days after reserpine treatment was started, the animals were transferred to metabolism cages where temperature was maintained at 13°±5° C. Urine was collected over 24-hour periods and assayed for adrenaline and noradrenaline. Heart, spleen, and liver tissue were also assayed. Certain of the reserpinized rats were given 10 mg/kg phenoxybenzamine i.p. Adrenalectomized rats subjected to moderate cold exposure showed a significant increase in noradrenaline excretion in urine. Adrenalectomized rats, treated with reserpine, however, failed to respond with an increase in the noradrenaline excretion during cold stress. A fall in the noradrenaline excretion of the reserpinized animals was usually followed by death. The majority of rats given phenoxybenzamine died within 24 hours of administration of the drug. Results suggest that reserpine inhibits noradrenaline synthesis in vivo and that the survival of moderately cold-stressed adrenalectomized animals is related to the secretion of noradrenaline.

University of Toronto
Toronto, Ontario, Canada

- 2575** Gunne, Lars-M. Catecholamines and 5-hydroxytryptamine in morphine tolerance and withdrawal. *Acta Physiologica Scandinavica*, Supplement 204, 58:5-91, 1963.

A study was made of the effects of acute and chronic morphine administration and of withdrawal and nalorphine-induced abstinence on the general behavior of dogs, cats, and rats. Special attention was paid to species differences. A study was then made of the effects of chronic morphine treatment and abstinence on the brain content of noradrenaline, dopamine, and 5HT and on the adrenal gland content of adrenaline and noradrenaline. To obtain additional information concerning the rate of synthesis and liberation of the monoamines, a study was made of the urinary output of adrenaline, noradrenaline, and 5HIAA. Experimental methods and assay procedures are described in detail. Results link the appearance and development of the morphine abstinence syndrome with a liberation of brain catecholamines (noradrenaline and dopamine). The 5HT appears to remain unaffected by chronic morphine treatment and by withdrawal. (168 references)

Karolinska Institutet
Stockholm, Sweden

- 2576 Markiewicz, Lech. Biochemical and functional effects of long-term administration of reserpine in mice. *Acta Physiologica Scandinavica*, 58:376-380, 1963.

The biochemical and functional effects of chronic administration of reserpine were studied in mice given daily injections of 0.08 mg/kg reserpine for 80 days. Noradrenaline, dopamine, and 5HT were measured in the brain, noradrenaline in the heart, and adrenaline and noradrenaline in the adrenals. The behavior and the body weights of the mice were followed closely throughout the entire period of treatment. The major part of the tissue monoamines disappeared during the initial period of the injections, but there tended to be a recovery of the monoamines during the latter part of the experiment, in spite of continued injections with reserpine. The weight and the behavior of the mice also showed the typical actions of reserpine during the initial period of injections (i.e., weight loss and sedation), but as the injections continued these functions also showed at least a partial recovery.

University of Göteborg
Göteborg, Sweden

- 2577 Benmiloud, M. & v. Euler, U. S. Effects of bretylium, reserpine, guanethidine and sympathetic denervation on the noradrenaline content of the rat submaxillary gland. *Acta Physiologica Scandinavica*, 59:34-42, 1963.

The time course of noradrenaline depletion after sympathetic denervation in the rat submaxillary glands and the effects of bretylium, reserpine, and guanethidine on the noradrenaline content of the gland 12 hours after denervation, when partial depletion had occurred, were determined. Some aspects of the blocking action of bretylium on the noradrenaline-depleting effect of guanethidine and reserpine were also studied. Male Sprague-Dawley rats (270 to 350 g in weight) were used in all experiments. All drugs were given s.c. within 5 minutes after denervation. Subsequent doses of bretylium were given every 4 hours as indicated. Dosages were as follows: 50 mg/kg bretylium, 20 µg/kg to 30 µg/kg reserpine, and 20 mg/kg guanethidine. After sympathetic denervation, the noradrenaline content of the rat submaxillary gland decreased slowly during the first 8 hours and disappeared completely in 24 hours. Reserpine and guanethidine caused

depletion of noradrenaline from denervated as well as innervated glands. In the case of reserpine, the denervated gland was slightly less depleted ($p < 0.05$). The noradrenaline depletion produced by treatment with these two drugs and by sympathetic denervation was significantly reduced by simultaneous injection of bretylium. Bretylium given alone also decreased the noradrenaline content in both denervated and innervated glands, but not to the same extent as reserpine and guanethidine. The implications of these results are discussed.

3 Rue des Cèdres
Algiers, Algeria

- 2578 Angelakos, E. T. & Torchiana, M. L. Positive inotropic responses and catecholamine content of isolated rabbit atria exposed tyramine. *Acta Physiologica Scandinavica*, 59:161-168, 1963.

The inotropic effects of tyramine were studied using isolated rabbit atria; catecholamine determinations were made in the same atria to provide a direct evaluation of the possible correlation between tyramine inotropic effects and catecholamine release. The left atria from male albino rabbits was removed and placed in a tissue bath; tyramine was added to the carbogen-aerated perfusion solution. The noradrenaline (NA) content of isolated rabbit atria was essentially unchanged following perfusion with tyramine (100 µg/ml) for 30 minutes. Over the same period, the positive inotropic effect of tyramine was still 75% of the peak response. After prolonged exposure (2 to 3 hours), the NA content decreased about 25% and the inotropic effect about 50%. In general, there was a correlation between the reduction in the response to tyramine and the NA content. However, the NA content was still 40% to 50% of the control value when the tissue no longer responded to tyramine. At that time, the tissue was fully responsive to administered NA. The release of NA tissue content could not supply more than a total of 0.1 µg to 0.2 µg NA over 2 to 3 hours. This suggests a considerable synthesis of NA in vitro if the effect of tyramine is indeed mediated through NA release. Direct measurement showed that 30 minutes after the end of a prolonged tyramine infusion, the NA tissue content was restored by an amount corresponding to about 20% of the control value. This, however, did not restore the response to tyramine.

Karolinska Institutet
Stockholm, Sweden

2579 Slater, T. F. Studies on a succinate-neotetrazolium reductase system of rat liver. II. Points of coupling with the respiratory chain. *Biochimica et Biophysica Acta*, 77:365-382, 1963.

In the first part of this series, the reduction of neotetrazolium (NT) by rat-liver tissue in the presence of succinate did not increase linearly with the amount of tissue. The present work attempts to establish whether this nonlinear response is, in fact, due to the presence of a diffusible endogenous electron carrier linking succinate oxidation to neotetrazolium reduction and, if so, to ascertain its nature. Rat-liver homogenates were prepared from adult, female, albino rats. Tables give the effects of quinol, benzoquinone, naphthoquinone, vitamin K₃, ubiquinone, dicumeol, phenazine, dinitrophenol, manganese chloride, urethane, salicylate, chlorpromazine, trifluoperazine, chlordiazepoxide, cytochrome C, *p*-chloromercuribenzoate, amytal, Co²⁺, and diethylstilbestrol and their controls on the succinate-NT reductase system of rat-liver homogenates under aerobic assay conditions; the effects of vitamin K₃, ubiquinone, azide, dicumerol, cytochrome C, Na N₃, hydroxylamine, and sodium cyanide under anaerobic conditions; and the effects of antimycin A under aerobic and anaerobic conditions and in the presence of vitamin K₃ and cytochrome C. The nonlinear response of the succinate-neotetrazolium reductase system is partly dependent on the oxygen level in the incubating medium, but is not affected by cytochrome oxidase inhibitors. It is suggested that, in this system, neotetrazolium chloride is mainly reduced via an interaction with a factor that is sensitive to oxygen and that couples neotetrazolium chloride with the respiratory chain. The results obtained allow the sites of interaction of neotetrazolium chloride with the respiratory chain to be determined. Under aerobic conditions, 90% of the neotetrazolium is reduced near cytochrome C via the factor described above, and 10% is reduced near ubiquinone. Under anaerobic conditions, the relative proportions of these two sites change so that neotetrazolium is reduced approximately 50% at each site.

Department of Clinical Pathology
University College Hospital Medical School
London, England

2580 Slater, T. F., Sawyer, Barbara, & Sträuli, Ursula. Studies on succinate-tetrazolium reductase systems. III. Points of coupling of four different tetrazolium salts. *Biochimica et Biophysica Acta*, 77:383-393, 1963.

The localization of the coupling points of four different tetrazolium salts—*C*, *N*-diphenyl-*N'*-4,5-dimethylthiazol-2-yl tetrazolium bromide (MTT), 2-*p*-nitrophenyl-3-*p*-iodophenyl-5-phenyltetrazolium chloride (INT), triphenyltetrazolium chloride (TTC), and nitro-blue tetrazolium (NBT)—with the respiratory chain was established. Liver tissue suspensions of adult, female, albino rats in 0.15 ml of each tetrazolium salt were tested with various respiratory-chain inhibitors in order to localize where the salts were reacting with the chain. The reaction of NBT (0.5% (w/v) aqueous solution) was insensitive to the presence of antimycin A or to the level of oxygen in the incubation mixture. This suggests that NBT acts almost completely at one site on the respiratory chain, possibly at the level of ubiquinone. The MTT (0.5% (w/v) aqueous solution) appeared to react at two sites, one of which was sensitive to antimycin A in the region of cytochrome C. The TTC (1% (w/v) aqueous solution) reacted with the terminal oxidase, and INT (0.5% (w/v) aqueous solution) reacted in a manner similar to MTT.

University College Hospital Medical School
University Street
London, England

2581 Giuditta, Antonio & Di Prisco, Guido. The inhibition of cerebral NAD(P)H:(acceptor) oxidoreductase by barbiturates and nervous depressants. Relationship with chemical structure. *Biochimica et Biophysica Acta*, 77:394-407, 1963.

The barbiturate inhibition of nicotinamide nucleotide NAD(P)H dehydrogenase I has been examined and compared from the point of view of its structural requirements with that of other enzymic systems, such as mitochondria. The compounds used were phenobarbital, amylobarbitol, pentobarbital, cyclobarbitol, butobarbital, barbital, azetidinone, oxazindione, *N*-methyloxazindiones, methylphenobarbital, methoin, and glutethimide. The NAD(P)H dehydrogenase I was extracted from fresh ox brain, and beef heart mitochondria were used. Cerebral NAD(P)H dehydrogenase is inhibited by barbiturates and nervous depressants that compete with

the substrate. Determination of K_i values for each compound provides a quantitative measure of their inhibitory effect. The importance of the $-CO-NR-$ group and of the size of substituent groups is discussed. Other groups of atoms, can, however, substitute for $-CO-NR-$. Cyclic structures are not required for inhibition. A parallel investigation on the structural requirements for inhibition of NADH oxidase of heart mitochondria has revealed a general similarity in the chemical structures required. The possible nature of inhibitory groups involved in binding with the enzyme is discussed.

The International Laboratory of
Genetics and Biophysics
Naples, Italy

2582 Bohdanecký, Z. & Nečina, J. **Course of some pharmacological tests in functionally decorticated animals.** *Physiologia Bohemoslovenica*, 12(1):55-61, 1963.

A variety of pharmacological tests were performed in rats and mice functionally decorticated by Leão's EEG spreading depression to demonstrate the advantages of decortication by spreading depression over surgical decortication. White mice (Konárovice) of both sexes (16 to 20 g in weight) and male Wistar rats (180 to 200 g in weight) were used. The technique for inducing spreading cortical depression is described. The following pharmacological tests were performed in the decorticated animals: effect on thiopental, hydroxydione, magnesium sulfate, and ether anesthesia; effect on amphetamine group toxicity; alteration of convulsant threshold for caffeine, pentylenetetrazol, and strychnine; effect on atropine and cepentyl mydriasis; and effect on phenylbutazone, chlorpromazine, pethidine, and morphine analgesia. During spreading depression, thiopental, hydroxydione, and ether anesthesia were prolonged, but $MgSO_4$ anesthesia was shortened; the convulsive threshold for caffeine pentylenetetrazol, and strychnine was raised; group toxicity to amphetamine was not affected; the sensitivity of the animals to the four analgesics increased; and atropine mydriasis, but not cepentyl mydriasis, was potentiated. Spreading depression appeared to be a useful adjunct to routine pharmacological testing.

Research Institute for Natural Substances
Prague, Czechoslovakia

2583 Votava, Z. & Lamplová, I. **Some pharmacological effects of lysenyl and its stereoisomers.** *Physiologia Bohemoslovenica*, 12(1):37-42, 1963.

Results of the pharmacological testing of *N*- α -6-methylisoergolenyl-8-*N',N'*-diethylurea (lysenyl) and its stereoisomers, α -ergolenyl, *L*-isoergolenyl, and *L*-ergolenyl, are reported. The following tests were performed: acute toxicity in mice, rats, and rabbits; mydriatic effect in mice; potentiation of thiopental anesthesia in mice; uterotonic effect in rabbits; effect on blood pressure in chloralose--pentobarbital-anesthetized dogs; and antiserotonin effect in rats by Vane's method (1957) and by the method of Doepfner and Cerletti (1958). Lysenyl had, by far, the most marked antiserotonin effect; the drug also produced the greatest potentiation of thiopental anesthesia and the most pronounced hypotonic effect. The *L*-isoergolenyl was the most toxic and *L*-ergolenyl the least toxic. The α -ergolenyl had the greatest mydriatic effect.

Research Institute of
Pharmacy and Biochemistry
Prague, Czechoslovakia

2584 Psychoyos, A. **A study of the hormonal requirements for ovum implantation in the rat, by means of delayed nidation-inducing substances (chlorpromazine, trifluoperazine).** *Journal of Endocrinology*, 27:337-343, 1963.

The effects of trifluoperazine and chlorpromazine on nidation were studied in Wistar rats (180 to 220 g in weight). The effects on nidation were studied in the following three series of experiments: (1) daily treatment with trifluoperazine; (2) a single injection of trifluoperazine given before ovariectomy; and (3) a single injection of chlorpromazine given before ovariectomy. Trifluoperazine was more effective than chlorpromazine in producing delayed nidation. When trifluoperazine treatment was started at a dose of 20 mg/kg on the 3rd day of normal pregnancy and repeated every 24 hours at a dose of 10 mg/kg to the 14th day of pregnancy, delayed nidation occurred in over 80% of the animals. Implantation was induced by 0.1 μ g estradiol. A single 20 mg/kg dose of trifluoperazine given to rats subsequently spayed and treated with progesterone post-pones for at least 24 hours the stage at which ovariectomy is compatible with ovum implantation. Animals given 20 mg/kg

chlorpromazine implanted normally, but nidation was delayed in 5 of 7 animals given 40 mg/kg of the drug. The results obtained support the hypothesis that nidation is induced, under normal conditions, by a release of estrogen on the fourth day of pregnancy. It is suggested that tranquilizers influence ovum implantation by postponing, through the pituitary cycle, this discharge of estrogen.

Collège de France
Paris, France

- 2585 Nishinuma, K. (Monoamine oxidase inhibitors as antidepressants.)
Psychiatria et Neurologia Japonica, 65:614-619, 1963.

In this study, MAO activity was determined by: (1) a monometric method of measuring oxygen uptake, using tyramine as a substrate in the presence of potassium cyanide; (2) measurement of disappearance of the substrate; and (3) fluorometric assay of an increase of endogenous catecholamines in the brain. Significant inhibition of the brain MAO by small doses of MAO inhibitors was observed only after a long-term administration, but was not observed after a single administration. A new substance, piperonylisopropylhydrazine, was synthesized and studied biochemically. It was found to possess a potent inhibitory action on MAO in vitro and in vivo. With a small dose, the substance inhibited the brain MAO in the long-term administration; this was confirmed by an elevation of endogenous norepinephrine level in the brain. In the long-term experiments with a small dose (0.5 mg/kg), brain MAO was more intensely inhibited than was the liver MAO. No pathological changes were revealed in the several tissues, including the liver, taken from animals in which there had been long-term administration of the substance, either 0.5 mg/kg for 14 days or 30 mg/kg for 6 months. The new substance is expected to prove a useful antidepressant that has no serious side effects related to the liver.

(No address)

- 2586 Kajitani, T. (Electroencephalographic studies of mentally retarded children. Part I. Effects of various psychotropic drugs on the electroencephalograms of mentally retarded children.)
Psychiatria et Neurologia Japonica, 65:211-223, 1963.

Six different types of psychotropic drugs were administered orally and parenterally to mentally-retarded children, ranging in age from 5 to 17 years, in order to study the drugs' effects on the clinical picture and EEG of these children. Using a histogram and an automatic frequency analyzer, the following results were obtained: (1) Methylphenidate decreased δ and θ waves and increased α waves; pheniprazine increased θ and decreased β waves; imipramine increased δ waves and decreased α waves; reserpine increased θ waves; GABOB decreased δ waves and increased α waves; and chlórdiazepoxide decreased δ and θ waves and increased β waves. (2) Paroxysmal discharges were activated markedly by imipramine and slightly by methylphenidate, reserpine, and GABOB; they were inhibited markedly by chlórdiazepoxide and slightly by pheniprazine. (3) The degree of buildup by hyperventilation tended to be increased by methylphenidate, imipramine, and reserpine. In the groups given pheniprazine and GABOB, practically no difference was noted in the degree of buildup before and after administration. In the group administered chlórdiazepoxide, the degree of buildup tended to decrease following the administration. (4) The response of the occipital basic waves to the eye-opening-and-closing test was improved by methylphenidate, reserpine, and GABOB, but it was aggravated by imipramine and chlórdiazepoxide. Pheniprazine had no effect at all in this test. (5) The photic driving produced by photic stimulation was accelerated by imipramine, reserpine, and GABOB. Chlórdiazepoxide tended to have an inhibitory action upon the photic driving. (6) The effects of these drugs on the EEG of the normal controls were of the same types as in the mentally retarded, but they were far less intense in the controls.

Okayama University
School of Medicine
Okayama, Japan

2587 Příbylová, H. & Znamenáček, K.

Changes in some functions of the newborn following the administration of chlorpromazine. Review of Czechoslovak Medicine, 9(2):94-102, 1963.

The effect of chlorpromazine on oxygen consumption, respiratory rate, rectal and skin temperatures, vocal manifestations, and pulse rate was studied in 38 full-term neonates. Chlorpromazine (2 mg/kg 24 hours) was administered p.o. in environmental temperatures of 22° to 24° C or 19° C. Compared to the controls, there was no significant effect on oxygen consumption, rectal temperature, and respiratory rate in the other neonates in an environmental temperature of 22° to 24° C. However, with the lower environmental temperature, a decline in oxygen consumption occurred and also a fall in the average respiratory rate, but it rose in three of the babies. There was a mild state of inhibition that was the same in both groups; this condition disappeared after 3 to 5 hours. A single dose of 0.6 mg/kg of chlorpromazine was given to two groups of babies in the same environmental temperatures as in the previous experiments. There was a mild fall in oxygen consumption, respiratory rate, and rectal temperature; the skin temperature remained unchanged, and the pulse rate was slightly increased when the environmental temperature was 24° C. The depth of inhibition was greater than in the previous groups. At 19° C, no further changes occurred. There were signs of dyspnea and periodic changes of respiratory rhythm in these babies. The inhibition was shallower in these babies than in those in an environmental temperature of 24° C. There were no changes observed in neonates whose mothers had been given chlorpromazine during labor.

Institute for the Care of Mother and Child
Prague, Czechoslovakia

2588 Vávra, J. & Mydlil, V. **Influence of chlorpromazine on ventilation and oxygen consumption in newborn infants.** Review of Czechoslovak Medicine, 9(3):189-196, 1963.

The influence of a single dose of chlorpromazine i.v. (1.5 mg/kg body weight) on the respiration rate, respiratory volume, respiratory minute volume, character of spirogram, and the oxygen consumption has been studied in newborn babies to obtain more detailed knowledge of this drug's pharmacodynamic effects. A total of seven

infants were examined in a whole-body plethysmograph, with five normal infants and two pathological cases (perinatal injury of the CNS). Respiration underwent marked changes after the administration of chlorpromazine. After brief excitation, inhibition set in with the most typical sign—prolonged Cheyne—Stokes breathing and a slowing down of the respiration rate, a mild decrease of the minute respiratory volume, and an increase in the average respiratory volume. In several instances, particularly in those infants with perinatal damage of the CNS, gross irregularities with apnoeic intervals, apneusis, or very irregular respiration with occasional deep inspiration were observed. If the body temperature is kept normal, the oxygen consumption is not influenced to an extent to exceed the error of the method and of individual short-term variations of oxygen consumption.

Charles University
Prague, Czechoslovakia

2589 Denys, Annette, Lévy, Jeanne, & Michel-Ber, Estera. **Contribution à l'étude du mécanisme de l'action antidépressive des inhibiteurs de la monoamine-oxydase (MAO) au niveau du système nerveux central de la souris. II. Influence de quelques dérivés de la pyridoxine sur l'action antidépressive des MAO. (The antidepressive activity of monoamine oxidase (MAO) inhibitors on the central nervous system of the mouse. II. The effect of certain pyridoxine derivatives on this activity.)** Journal de Physiologie, 55:381-404, 1963.

To investigate the phenomenon of antagonism previously observed between pyridoxal-5-phosphate (P5P) and various MAO inhibitors in the presence of *d,l*-DOPA and reserpine and to determine more precisely the role played by P5P, the effect of combinations of these compounds on the duration of chloralhydrate-induced sleep was studied in Swiss mice. The P5P was given in combination with MAO inhibitors and DOPA (or *d,l*-metatyrosine) and MAO inhibitors plus reserpine; in some experiments, pyridoxine derivatives were given in place of P5P. The P5P reversed the arousal produced by DOPA and *d,l*-metatyrosine in the presence of MAO inhibitors and reestablished the potentiation of sleep by reserpine, which the MAO inhibitors had suppressed. The oxidized, nonphosphorylated compound, pyridoxal, produced the same effects as P5P, but the monoxidized, phosphorylated compound, pyridoxamine-5-phosphate, was inactive. Evidence suggested that the MAO inhibitors

interfere with the enzymatic oxidation of pyridoxine derivatives rather than block the enzymatic phosphorylation of pyridoxal. The site of action of MAO inhibitors on pyridoxal phosphokinase and pyridoxamine-5-phosphate oxidase is discussed.

Chemical Pharmacology Laboratory
University of Paris Medical School
Paris, France

- 2590 Buchel, L., Lévy, Jeanne, & Tanguy, O. Importance des phénomènes d'antagonisme et de synergie dans l'étude pharmacologique des neuroleptiques. (Importance of antagonism and synergism in pharmacological study of centrally acting drugs.) *Journal de Physiologie*, 54:771-786, 1963.

The antagonistic and synergistic activities of three centrally acting drugs (chlorpromazine, reserpine, and triperidol) were determined in a variety of pharmacological tests in mice. Various doses of the drugs were given to determine their effect on exploratory activity and motility, the toxicity of *D*-amphetamine in grouped mice, convulsive crises induced by cocaine and caffeine, experimental sleep produced by chloral hydrate, and analgesia produced by methadone. Chlorpromazine, in doses that produced no change in behavior when given alone, antagonized *D*-amphetamine and cocaine and prolonged experimental sleep. Triperidol, in doses that produced no change in behavior when given alone, exerted a depressive action in the presence of *D*-amphetamine and caffeine. In doses that produced some change in activity when given alone, triperidol antagonized cocaine and prolonged experimental sleep. Reserpine was ineffective in a combination with other drugs in doses that produced no change in activity when given alone. The importance of determining antagonistic and synergistic phenomena in the pharmacological analysis of centrally active drugs is stressed.

Laboratory of Chemical Pharmacology
University of Paris Medical School
Paris, France

- 2591 Piha, R. S., Bergström, R. M., Bergström, L., Uusitalo, A. J., & Oja, S. S. Studies in the metabolism of brain proteins. II. Effect of chlorpromazine and lysergic acid diethylamide on the turnover rate of rat brain proteins. *Annales Medicinæ Experimentalis et Biologiæ Fenniae*, 41:498-515, 1963.

The effect of chlorpromazine and LSD-25 on the turnover rates of two fractions of proteins was studied in the cerebral cortex, cerebellum, basal ganglia, and pons medulla of the rat brain. A total of 78 healthy, male and female rats (200 to 350 g in weight) was used—20 on chlorpromazine, 12 on LSD-25, and the remainder as controls. Chlorpromazine, 20 to 50 mg/kg/day, was injected i.m. and 0.1 mg/kg LSD-25 b.i.d. was injected i.m. on three successive days before injection of C¹⁴-amino acid, and then continuously throughout the experimental period. Chlorpromazine lengthened the time for the brain proteins to reach their maximum radioactivity in all the brain areas except the pons medulla; decreased the maximum specific activities of the supernatant proteins on average by 23% and those of the precipitate proteins on average by 39%, the inhibition being greatest in the basal ganglia in both fractions; and slowed up the initial rate of elimination of labeled proteins until the third day, the subsequent disappearance of radioactivity occurring faster than normal. The LSD-25 shortened the time for the brain proteins to reach their maximum radioactivity in all other brain areas except the cerebellum, decreased the maximum specific activities in both fractions by about 17%, increased the initial rate of elimination of the labeled proteins in the basal ganglia and pons medulla, but decreased it in the cerebral cortex and cerebellum, the subsequent rate of protein destruction being normal. Protein synthesis in the four functional areas of the brain is inhibited by chlorpromazine, the degree of the inhibition decreasing in the following order: basal ganglia, pons medulla, cerebellum, and cerebral cortex. The mechanism of the inhibitory effect of chlorpromazine on the synthesis and turnover of proteins in the brain and the effect of LSD-25 on brain protein metabolism are considered.

Department of Physiology
University of Helsinki
Helsinki, Finland

2592 Lagerspetz, Kari & Tirri, Rauno.

The induction of physiological tolerance to promazine in mice. III. Respiratory enzymes in the brain in induced tolerance. *Annales Medicinae Experimentalis et Biologiae Fenniae*, 41:315-318, 1963.

It has been suggested that the development of tolerance induced by promazine involves an increase in the activity of the respiratory enzymes, e.g., in the activity of the dehydrogenases in the brain. The respiration of brain cortex slices with pyruvate as the substrate was 20% higher in animals that received promazine. This study was carried out in attempt to further elucidate the mechanism of promazine-induced tolerance. Albino male mice (4 months of age) were given promazine (10 mg/kg s.c.) for 20 to 25 or 40 to 45 days. The control groups received an injection of Ringer's solution daily. The activity of the succinic dehydrogenase complex and of the cytochrome C oxidase as well as the flavin adenine dinucleotide (FAD) concentration was measured in brain homogenates of control and promazine-tolerant mice. There were no significant differences in the enzyme activities or the FAD levels between the brain homogenates from the tolerant and from control animals.

Department of Zoology
University of Turku
Turku, Finland

2593 Piha, R. S., Oja, S. S., & Uusitalo, A. J. The effect of chlorpromazine on free amino acids in the rat brain. *Annales Medicinae Experimentalis et Biologiae Fenniae*, Supplement 5, 40:1-28, 1962.

The distribution of 14 amino acids or other amino compounds was examined by paper chromatography in whole-brain homogenates and in four separate areas of the brain, the cerebral cortex, the cerebellum, the pons-medulla and the interior of the cerebrum of 76 male and female rats (200 to 300 g in weight), of control rats, and of rats injected with chlorpromazine s.c. (30 mg/kg the first day; 50 mg/kg on 3 successive days). In addition, the α -amino nitrogen content of the protein-free extracts was determined. In the control group, the concentration of α -amino nitrogen decreased in the following order: cerebral cortex, cerebellum, interior of the cerebrum, and pons-medulla. In the control rats, the cerebral cortex contained higher concentrations of glutamic acid, aspartic acid, ethanolamine phosphate, and GABA than did any other areas of the brain. Glutathione and taurine were found in the

cerebellum in larger amounts than elsewhere, glutamic acid and aspartic acid taking second place. The pons-medulla and the interior of the cerebrum contained smaller amounts of amino acids than did the other two areas. In the whole-brain homogenates, no significant change was found in the concentration of α -amino nitrogen after the administration of chlorpromazine. A slight decrease in the concentrations of most of the amino acids was noted in the whole-brain homogenates obtained from chlorpromazine-treated animals. The depressing effect of chlorpromazine on the content of individual amino acids was stronger in those areas where the chlorpromazine content was higher, in the cerebral cortex (99 μ g/g) and the cerebellum (78 μ g/g), than in the pons-medulla (60 μ g/g) and in the interior of the cerebrum (49 μ g/g). Chlorpromazine significantly lowered the amounts of glutamic acid, GABA, serine and glycine, aspartic acid, and ethanolamine phosphate in the cerebral cortex. The cerebral cortex was the only region in which an appreciable rise in the alanine content was shown. In the cerebellum, the contents of glutamic acid, GABA, serine and glycine, alanine, and taurine were decreased; also, there was no increase in any of the amino acids studied. In the brain stem and medulla, chlorpromazine had a slight effect on the amino acid content. A significant fall was found only in the case of alanine. In the interior of the cerebrum, chlorpromazine depressed the concentrations of alanine and taurine considerably, and the aspartic acid and glutamine contents increased. The possible causes of the changes in the concentrations of amino acids and the relationship of the amino acid status to protein formation in the brain are discussed.

University of Helsinki
Helsinki, Finland

2594 Piha, R. S., Uusitalo, A. J., & Oja, S. S. Incorporation of ^{14} C-labelled amino acids into the proteins of the liver. Effect of chlorpromazine, meprobamate and lysergic acid diethylamide. *Annales Medicinae Experimentalis et Biologiae Fenniae*, 41:73-87, 1963.

The rate of incorporation of C^{14} -labelled amino acids, obtained by hydrolyzing C^{14} -*chlorella* protein, into the proteins of the supernatant and precipitate fractions separated from liver homogenates at 4,000 g for 30 minutes, and their subsequent turnover were studied in healthy untreated rats and rats of either sex (140 to 340 kg in weight) injected with chlorpromazine (25 to 50 mg/kg), meprobamate (200 to 400

mg/kg), or LSD (0.1 mg/kg) b.i.d. on 3 successive days before the C^{14} -amino acid injection. For comparison, the incorporation of the labelled amino acids into the plasma proteins and the rate of disappearance of C^{14} from the plasma proteins are described. In the control group, at 24 hours after the C^{14} injection, the specific activities of the proteins in the liver supernatant and precipitate fractions were on an average of 48.0% and 55.5%, respectively, of the isotope content of total plasma proteins. In normal rats the maximum specific activity was attained at 2 hours in both fractions. The half-lives of the most rapidly metabolized fractions in the supernatant and precipitate fractions were 1.8 and 1.1 days, respectively. The metabolically slower fractions turned over at rates corresponding to half-lives of 6.2 and 5.6 days, respectively. Chlorpromazine lengthened the time for the liver proteins to reach their maximum activity (12 hours for the supernatant fraction and 24 hours for the precipitate fraction), decreased the maximum specific activity in both fractions, and slowed up the rate of the most rapidly metabolized fractions, followed by a most faster rate of elimination than in controls. The LSD lowered the rate of the C^{14} incorporation and caused a rapid initial elimination in the precipitate fraction, followed by a normal rate of protein elimination, but the rate increased slightly during the elimination of the supernatant proteins. Meprobamate had no effect on the incorporation of amino acids into liver proteins in these 24-hour experiments. The plasma protein turnover was not substantially affected by LSD or meprobamate, but chlorpromazine delayed the incorporation of amino acids into plasma proteins and lengthened the time for them to reach their maximum activity.

University of Helsinki
Helsinki, Finland

2595 LaRue, Lucien & Gosselin, Jean-Yves.
L'apport du diazepam (Valium)
à la psychiatrie moderne. (The value of
diazepam (Valium) in modern psychiatry.)
Laval Medical, 34(10):1208-1220, 1963.

Diazepam was tested in 187 selected psychiatric patients, including 58 males and females from the psychiatric clinic of a general hospital and 129 males from a psychiatric hospital. Of the 187 patients, 24 received diazepam as their sole medication. The remaining 163 patients received diazepam combined with neuroleptics or

other medication. Diazepam dosage varied according to individual need. Results are tabulated. Of the 24 patients who received diazepam as sole medication, 93% of the neurotics and 50% of the psychotics (mostly schizophrenics) improved. In the 163 patients who received diazepam in combination, the drug appeared to complement or potentiate the medication already being given, particularly in refractory cases. Side effects, including ataxia, nausea, constipation, and excitation, were encountered in some patients when diazepam was given in excess of 15 mg daily.

Hospital of St. Michael the Archangel
Quebec, Canada

2596 Gschlacht, V. E. Ambulante
Behandlung psychisch Kranker mit
dem neuen Psychopharmakon Valium "Roche".
(Outpatient treatment of mental patients with
a new drug, Valium (Roche).) Schweizer
Archiv für Neurologie, Neurochirurgie und
Psychiatrie, 92(1):193-203, 1963.

Diazepam was tested in 75 patients, 33 males and 42 females, 20 to 75 years of age. The patient sample included 40 cases of psychogenic reaction, 27 of psychogenic development 6 of depression, and 2 of dementia. Diazepam was given orally in single doses of 5 to 30 mg or in daily doses of 5 to 20 mg t.i.d.; in exceptional cases, up to 80 mg/day was given. Duration of treatment was 2 days to 1 year. Onset of action after oral administration occurred within 30 minutes and lasted for 4 hours or more. Improvement in the 75 patients was 42 good, 22 moderate, and 11 insignificant or none. Seven case histories are summarized. A true antidepressant action was not established for diazepam, but its combination with thymoleptics enabled depression to be more adequately treated. No untoward effects occurred. Five patients complained of slight diurnal tiredness, and one reported weakness of the legs, but these were relieved by reducing diazepam dosage. The sedative, antianxiety, and muscle-relaxing properties of diazepam were more potent than were those of chlordiazepoxide.

Krummackerstrasse 12
Bottmingen bei Basel, Switzerland

2597 Blumberg, Arnold G. **Effect of chlorpromazine with procyclidine and imipramine on radioactive iodine uptake.** *Journal of Clinical Endocrinology and Metabolism*, 23:881-884, 1963.

A double-blind study was conducted to test the effect on the radioactive iodine uptake of the thyroid gland of imipramine and chlorpromazine plus procyclidine on 122 psychiatric patients in an open-ward voluntary psychiatric hospital. The diagnoses of the patients were as follows: schizophrenia (67), affective psychosis (43), and psychoneurosis (12). Thirty-four patients were given placebo, and 43 were treated with imipramine, starting with 75 mg/day and increasing weekly to 300 mg/day. Thirty-nine patients were treated with the mixture of chlorpromazine (300 mg/day increasing to 1,200 mg/day) and procyclidine (3.75 mg/day increasing to 15 mg/day). A group of six patients received procyclidine alone (3.75 mg/day increasing to 15 mg/day). The three drugs were studied simultaneously. A 24-hour radioactive iodine uptake test was carried out on each patient before treatment and was repeated after 5 weeks of treatment. All tests were conducted using a 15 μ c test dose of carrier-free radioactive iodine and counting the patient's neck from four geometric portals. An increase of over 5% in radioactive iodine uptake occurred in the following groups of patients: 4 placebo, 14 imipramine, 28 chlorpromazine plus procyclidine, and 1 procyclidine. No change or decrease was observed in the following groups of patients: 30 placebo, 29 imipramine, 11 chlorpromazine plus procyclidine, and 5 procyclidine. Patients treated with a mixture of chlorpromazine plus procyclidine, in large doses, showed a significant rise in the thyroidal uptake of radioactive iodine; imipramine-treated patients showed less uptake.

Hillside Hospital
Glen Oaks, Long Island, New York

2598 Breitner, Carl. **Appetite suppressing drugs as an etiologic factor in mental illness.** *Psychosomatics*, 4:327-337, 1963.

A brief review is given of literature concerning the hazards of amphetamines with respect to mental health. A list of the amphetamines is given, and their chemistry, physiology, and pharmacology are discussed. The pharmacological effects are alertness, wakefulness, blanching of mucous membranes,

vasoconstriction, muscle tone and contractility increase, reduced fatigue, peripheral reflex increase, mild analgesic action, and increased blood-pressure and blood-sugar levels. The specific mechanism of the amphetamines as an appetite suppressant is the inhibition of the lateral food-intake center of the hypothalamus. Seven case histories are cited as examples of the following psychotic reactions to the drugs: paranoid delusions, severe depression, withdrawal alternating with excitement, hypertension, and extreme excitation, emotional turmoil, urges to kill, and depression alternating with aggressiveness. The serious adverse reactions appear after various lengths of time, and improvement is slow even after drug withdrawal.

1515 North 9 Street
Phoenix, Arizona

2599 Pritchard, E. T. & Rossiter, R. J. **Formation of phosphatides from C¹⁴-labelled precursors in rat brain slices. Effect of chlorpromazine.** *Canadian Journal of Biochemistry and Physiology*, 41:341-345, 1963.

The effect of chlorpromazine on the incorporation of radioactivity from C¹⁴-labeled precursors into the phospholipids of slices of rat brain was investigated. Chlorpromazine (0.1 mM) caused an increase in the incorporation of radioactivity from glycerol-1-C¹⁴, glycine-2-C¹⁴, and serine-3-C¹⁴ into the phospholipids of the slices. There was no increase in the incorporation of radioactivity from choline-1,2-C¹⁴ or ethanolamine-1,2-C¹⁴. The effect of chlorpromazine on the individual phosphatides was examined and was found to be as follows: an increase in the incorporation of radioactivity from glycerol-1-C¹⁴ into phosphatidic acid and phosphatidyl serine, with no change for lecithin and phosphatidyl ethanolamine. Higher concentrations of chlorpromazine (1.0 mM) either inhibited (glycerol-1-C¹⁴, choline-1,2-C¹⁴), did not significantly alter (glycine-2-C¹⁴, ethanolamine-1,2-C¹⁴), or stimulated (serine-3-C¹⁴) the incorporation of radioactivity into phospholipids.

Department of Biochemistry
University of Western Ontario
London, Ontario, Canada

2600 Scott, K. G. & Daniels, A. E. The similar action of lysergic acid derivatives, Hypertensin (Ciba) and Aldosterone upon ^{86}Rb uptake by red blood cells from control and cancer subjects. Proceedings of the Western Pharmacology Society, 6:42, 1963.

Studies with rats bearing transmissible fibrosarcoma were performed in order to relate the action of cancerous growths upon the permeability of the membranes of normal cells. The red blood cell (RBC) was used as a model and rubidium-86 (Rb^{86}) was used as a tracer. The slow uptake rate of Rb^{86} by the RBC in rats bearing transmissible fibrosarcoma was also observed with RBC from tumor-bearing rats suspended in plasma from normal rats. This defect is remedied by the addition of either a 5HT and histamine blocker, SA-97 (*N*-chloro-benzhydryl-*N*¹-methyl-homopiperazine) or by a 5HT blocker, BOL (α -2-bromolysergic acid diethylamide). Angiotensin and aldosterone also shorten the Rb^{86} uptake in rats. A study with 10 patients has indicated that angiotensin is as effective in man as in rats. The minimal effective dosage in man is 0.1 $\mu\text{g}/\text{cc}$, 10 $\mu\text{g}/\text{cc}$, 100 $\mu\text{g}/\text{cc}$ blood for angiotensin, BOL, and SA-97, respectively and 0.0007 $\mu\text{g}/\text{cc}$, 0.04 $\mu\text{g}/\text{cc}$, and 0.083 $\mu\text{g}/\text{cc}$ blood, respectively, in the rat.

University of California
Medical Center
San Francisco, California

2601 Brodie, B. B. & Costa, E. Concept of the neurochemical transducer as an organized molecular unit at sympathetic nerve endings. *Activitas Nervosa Superior*, 5(3):264-279, 1963.

A model of the norepinephrine (NE) transducer was developed and used in studies of the mechanism by which MAO inhibitors lower blood pressure. The sympatholytic effects of two MAO inhibitors, phenelzine and pargyline, were compared with those of bretylium and BW 392C60. Pretreatment with phenelzine, pargyline, and BW 392C60 did not elicit a rise in blood pressure. These results suggested that the MAO inhibitors exerted some bretylium-like activity in preventing nerve impulses from releasing NE.

National Heart Institute
National Institutes of Health
Bethesda, Maryland

2602 Chatterjee, M. L., De, M. S., Pal, S., & Seth, D. Pharmacological studies on imipramine: Preliminary observations. *Bulletin of the Calcutta School of Tropical Medicine*, 11(1):18-19, 1963.

The effects of imipramine on the spontaneous mobility of mice and, in normal rats, the oxygen consumption of the brain, liver lipids, adrenal wet weight, and adrenal cholesterol were studied. The effects of the drug on the latter three items of rats under "restrain-stress" for 24 hours were also studied. Control rats and rats pretreated (24 hours) with 10 and 20 mg/kg imipramine i.p. were used. In mice, the spontaneous mobility of normal mice was not reduced. In normal rats, the drug reduced the oxygen consumption of the brain but did not reduce the normal wet weight and total cholesterol content of the adrenal glands significantly. In "restrain-stress" treated rats, imipramine inhibited only slightly the lipid mobilization of the liver, the increase of wet weight, and the depletion of adrenal cholesterol.

Calcutta School of Tropical Medicine
Calcutta, India

2603 Guttman, Helene N. & Friedman, Walter. Protozoa as pharmacological tools: The phenothiazine tranquilizers. *Transactions of the New York Academy of Sciences*, 26:75-89, 1963.

A general method for the construction of a model system for preclinical screening of drug effectiveness was described. Since there are obvious similarities between the soporific side effect of antihistamines and the major effect of tranquilizers, a series of tranquilizers were tested for their ability to immobilize *Tetrahymena pyriformis*. The antimobility activity of the phenothiazine tranquilizers toward *T. pyriformis* paralleled their clinical effectiveness. An increase in the percentage of cells on the bottom of the wells occurred as the duration of incubation with chlorpromazine (0.30 $\mu\text{moles}/\text{ml}$) increased. As the percentage of immotile cells and the length of exposure increased, the organelles and cells swelled. These results indicate an increase in the permeability of the cell membrane. It was suggested that there is no common sensitive site in *T. pyriformis* that is liable to attack by antimobility drugs. It was concluded that the use of the combination phenothiazine plus chemotherapy

may simplify the attack of extracellular parasites, leukemias, solid tumors, and intracellular parasites. (38 references)

Haskins Laboratories
New York, New York

- 2604** Shionoya, Shigehiko. **Electron microscopic study on the catecholamine metabolism in the human adrenal medulla.** Nagoya Journal of Medical Science, 26:60-70, 1963.

The ultrastructure and catecholamine metabolism of the human adrenal medulla were examined by electron microscopy in tissues from 16 patients with peripheral occlusive vascular disease, 3 of whom were taking nialamide and 4 of whom were taking reserpine. The patients on nialamide had been receiving 225 to 300 mg p.o. daily for 3 to 7 days before the operation, and reserpine patients had been receiving 2.5 mg s.c. 7 to 10 days before the operation. The appearance of the light and dark cells and the osmiophilic granules of the adrenomedullary parenchyma are described in the untreated patients. A swelling or ring-like modification of mitochondria was seen in the light cells of the nialamide-treated medulla; the swelling may be a form of mitochondrial degeneration due to toxic metabolites produced by nialamide inhibition of MAO localized in the mitochondria. Changes in the granules and granular endoplasmic reticulum in the light cells in reserpine-treated tissue are described. Reserpine appears to release catecholamines without any pronounced damage of the granules and limited membranes. The catecholamine-containing granules appear to form in the Golgi retion, and the catecholamines may be liberated from the granules in situ within the cells and probably transported rapidly out of the cells without accumulation in the extragranular cytoplasm.

Nagoya University
School of Medicine
Nagoya, Japan

- 2605** Kalliomäki, J. L. & Saarimaa, H. A. **Angiotensin skin test in normotensive subjects and the effect of some antihypertensive drugs on the test.** Cardiologia, 43:371-375, 1963.

The angiotensin skin test was applied to 70 normotensive and 5 hypertensive subjects to verify the previously determined normotensive range (30 minutes or less) for

duration of the angiotensin-induced skin wheal. The effect of some antihypertensive drugs on the skin test was also tested in the subjects. The subjects included 60 patients (29 women and 37 men) with various internal diseases, 10 healthy subjects (5 women, 5 men), and 5 female hypertensives. Drugs and dosage schedules were as follows: 1 mg/day reserpine for 5 days; 400 mg/day meprobamate for 3 days; 1,000 mg/day α -methyldopa for 5 days; 30 mg/day guanethidine for 3 days; 100 mg/day hydralazine for 3 days; and 40 mg/day pentapyrrolidine for 3 days. Duration of the wheal produced by injection of 0.1 μ g of angiotensin was recorded. The distribution of the angiotensin skin test duration in normotensives had a considerable range without any tendency to group on the range < 30 minutes, previously presented as a normotensive range of this test. No specific grouping of the results within the various groups of diseases included in this series was observed. Treatment with hydralazine caused a statistically significant shortening of the angiotensin skin test duration, and the shortening observed during treatment with guanethidine was significant at the 10-5% confidence level. Reserpine, meprobamate, α -methyldopa, and pentapyrrolidine had no constant effect on the angiotensin skin test duration. Intravenous infusion of α -methyldopa in hypertensive patients caused a distinct decrease in blood pressure and an increase in the peripheral skin temperature, but no constant changes in the angiotensin skin test duration were observed.

University of Turku
Turku, Finland

- 2606** Iwamoto, Takio & Sato, Tetsuo. **Effects of chlorpromazine, azacyclonol and chlordiazepoxide on brain catecholamine contents of stressed rats.** Japanese Journal of Pharmacology, 13:66-73, 1963.

A study was made of the inhibiting effects of chlorpromazine, azacyclonol, and chlordiazepoxide on the brain catecholamine levels of albino Wistar rats, 200 to 280 g in weight, after electric shock. The technique of catecholamine estimation was the same as that described by Bertler (1958). The three tranquilizing drugs were administered s.c. Chlorpromazine was administered in a single dose of 8 mg/kg, 1 hour prior to shock treatment. Chlordiazepoxide and azacyclonol were administered in single doses of 10 mg/kg. The pretreated animals were given an electric shock of 50 v/sec, with 10-second intervals between, for 4 hours. Control animals were not given an

electric shock. Animals were sacrificed by decapitation, and the whole brain was removed, homogenized, and centrifuged. The catecholamines in elute were determined fluorometrically. An aliquot of the effluent was assayed to obtain a sample. The samples were then read using a spectrofluorometer. The following results on the brain nor-adrenaline level were noted: in cases of stress alone, without drug administration, it rose significantly as compared to the physiological state; chlorpromazine showed no significant effect on it in normal situations, but in the stressed state, it greatly inhibited the elevation of the level; azacyclonol and chlordiazepoxide showed little or no inhibition on the elevation. No adrenaline was detected in rat brains under stress alone, physiological, and stress after pretreatment with the tranquilizing drugs.

Institute of Chemical Pharmacology
Hakkaido University
School of Medicine
Sapporo, Japan

2607 Hosoya, Eikichi & Akita, Haruo.
Catecholamine level in brain and the spontaneous activity of morphinized rats. *Keio Journal of Medicine*, 12(3): 127-130, 1963.

The relationship between changes in 5HT and catecholamine (CA) levels in the brain induced by pretreatment with various drugs and changes in spontaneous activity produced by morphine or nalorphine was studied in morphinized male albino, Wistar Imamichi rats (100 g in weight). The rats were given morphine twice daily for 7 weeks, in a maximum dose of 100 mg/kg/day after the 21st day. The following drugs were given i.p. at the stated times prior to the experimental dose of morphine or nalorphine: 1 mg/kg reserpine, 24 to 48 hours; 400 mg/kg α -methyl-m-tyrosine (α -MMT), 16 to 24 hours; 20 or 50 mg/kg 5HTP, 30 minutes; 1 mg/kg reserpine, 3 hours, plus 10 mg/kg pheniprazine, 30 minutes; and 10 mg/kg pheniprazine, 30 minutes. Results showed that CA levels have a close relationship to changes in spontaneous activity but 5HT levels do not. The CA levels, however, do not causally determine the increase or decrease in activity.

Keio University
Tokyo, Japan

2608 Federal Aviation Agency. The effects of a tranquilizer on body temperature. Higgins, E. Arnold, Iampietro, P. F., Adams, Thomas, & Holmes, D. D. Oklahoma City, Oklahoma, Civil Aeromedical Research Institute, Aeronautical Center, 1963, 5 p.

This investigation was designed to determine the effects of propiopromazine HCl on thermoregulatory ability in dogs exposed to three environmental temperatures. Forty-eight 2-hour experiments were conducted using four young adult mongrel dogs (11.5 to 16 kg in weight) each exposed twice, while untranquilized, to each of three environmental temperatures (4.4°, 23.9°, and 37.8° C) and exposed twice to each temperature while tranquilized with 2.2 mg/kg i.v. propiopromazine. Little difference was noted in rectal temperature response for tranquilized and untranquilized animals at 23.9° C. Tranquilized animals showed a greater decline in internal temperature at an environmental temperature of 4.4° C than controls and showed a rise in rectal temperature during heat exposure (37.8° C); control animals showed a decline. It was concluded that propiopromazine apparently interferes with heat loss and heat conservation due to a possible direct effect on the diencephalon.

Federal Aviation Agency
Civil Aeromedical Research Institute
Oklahoma City, Oklahoma

2609 Eyal, Z. & Eyal-Giladi, H. Growth-retarding and growth-promoting effect of chlorpromazine on developing *Amblystoma mexicanum* (axolotl) embryos. *Experimental Cell Research*, 29:394-399, 1963.

The effect of varying concentrations of chlorpromazine and periods of exposure on the size of normally developing axolotl embryos was studied. Three groups of embryos, each with a different initial developmental stage (Harrison's stages 10 to 11, 15 to 16, and 29 to 30), were immersed in different concentrations of chlorpromazine for varying periods of time and then transferred into tap water and reared up to Harrison's stage 46. From measurements of the surface area of the head of the experimental larva, the immersion period leading to maximal growth at each concentration of chlorpromazine was different for each concentration. At

3.5×10^{-6} M, the optimal immersion period was as long as 5 hours. At 113×10^{-6} M, the optimal immersion period was 1 hour or less. Prolongation of the immersion period resulted in the development of progressively smaller larva. It was suggested that the biphasic effect may involve changes in phorous:oxygen ratios as well as changes in mitotic activity.

Hadassah University Hospital
Jerusalem, Israel

2610 Willheim, Robert, O'Malley, Benedict B., Fluss, Paul, Dickson, Jean, & Auber, Mitzi. Further studies concerning carcinolysis. Experimental Medicine and Surgery, 21:154-158, 1963.

The ability of blood serum to dissolve mouse ascites tumor cells was investigated. The tumor cells of ascites showed, when exposed to blood serum, a slight paling of the center and a narrow and cytoplasmic rim (stage 1), a loss of shape (stage 2), a pale blue center and wide cytoplasmic rim (stage 3), and a completely digested cytoplasm (stage 4). Treated cells were then stained with methyl-green-pyronin or acridine-orange in order to detect changes in cancer cells. Animals whose serum had not exerted a lytic influence upon cancer cells were injected with 2 cc/day or mouse ascites fluid. In some cases, an increase in lytic activity was observed. A positive serum could in some cases be changed to a negative one by injection of 2 cc of commercial india ink. Some chemical substances (prochlorperazine, reserpine, and azacyclonol) were found to have strong carcinolytic saturated fatty acids (myristic acid) that increased with the length of the fatty acid chain. Those chemical substances that produced cellular damage in vitro did not prove equally effective in vivo.

(No address)

2611 Takayanagi, Issei. Phenothiazine derivatives. Relationship between peripheral and central actions. Arzneimittel-Forschung, 14(6):694-698, 1963.

A possible relationship between peripheral and central actions was studied in 15 phenothiazines and 2 α -sympatholytics. As representative of peripheral action, the antihistaminic, anticholinergic, and antiarterenergic activities of the compounds

were determined by studying their influence on cumulative log dose-response curves obtained with histamine, the parasympathomimetic furtrethonium, and the sympathomimetic noradrenaline. As representative of central action, the ability of these compounds to inhibit amphetamine-induced locomotor activity was tested. There was a definite correlation between the peripheral α -sympatholytic (antiarterenergic) activity and inhibition of amphetamine-induced locomotor activity, which is presumed to be linked to amphetamine's central arterenergic actions. The results suggest that there is an analogy between the arterenergic receptors in the peripheral nervous system and those in the CNS.

University of Nijmegen
Nijmegen, The Netherlands

2612 Yamuchi, I. (Changes in frequency distribution of minor tremor and EEG with the dosage of triflupromazine.) Brain and Nerve, 15:418-423, 1963.

Triflupromazine therapy was administered to 14 schizophrenic patients, and it was found to be effective in half of the cases. In three cases, the onset of Parkinson-like syndromes was observed. The MT (minor tremor) and EEG frequency-distribution patterns were observed in 7 of the 14 patients. Recordings were taken on four occasions at 5-day intervals—at pretreatment and at three intervals when dosage was increased to 50, 100, and 150 mg, respectively. A relationship appears to exist between the therapeutic effects and both the MT frequency distribution patterns and the ratings in the α -bands. No relationship could be found between the EEG frequency distribution and the therapeutic effectiveness of the drug.

(No address)

2613 Gözsy, B. & Kátó, L. Effect of levomepromazine on the anaphylactic and on the anaphylactoid reaction in rats. Indian Journal of Medical Research, 51(2):264-267, 1963.

Experiments were conducted to ascertain whether the levomepromazine inhibition of a dextran-induced formation of edema in the rat by the in vivo formation of a pharmacologically inert complex between dextran and the drug is specific for dextran-induced damage or similar in vivo

reactions. Sprague-Dawley rats of both sexes were injected with dextran (7.9 mg/kg i.v.), and the intensity of edema was registered. Rats were sensitized with horse serum and pertussis vaccine (1 ml each). Hypothermia was registered rectally. Levomepromazine was injected i.m. in doses ranging from 1 to 20 mg/kg. Levomepromazine prevented anaphylactic shock of rats in an optimal dose of 5 mg/kg. In sensitized rats, the compound 48/80-induced capillary response was also inhibited by the drug when rats were sensitized with horse serum. Levomepromazine inhibited the dextran-induced edema, but lost its pharmacological property to inhibit capillary response to compound 48/80. When the anaphylactoid reaction induced by dextran is inhibited by levomepromazine, the drug is bound quantitatively to the damaging agent, although it still retains its pharmacological properties in vivo in the anaphylactic shock induced by horse serum. The results suggest that the complex with dextran is rather specific and that levomepromazine does not interfere with other antigen-antibody reactions by this mechanism.

University of Montreal
Montreal, Canada

- 2614 Bente, D. *Elektroenzephalographie und psychiatrische Pharmakotherapie.* (Electroencephalography and psychiatric pharmacotherapy.) In: Achelis, J. D. & v. Dittfurth, H., eds. *Anthropologische und naturwissenschaftliche Grundlagen der Pharmako-Psychiatrie.* (Anthropological and scientific foundations of pharmacopsychiatry.) Starnberg Conferences, 1961. Stuttgart, Germany, Georg Thieme, 1963, p. 75-99.

There is no doubt that all psychopharmacological agents used to the present time exert an influence on the EEG. Different drugs and doses, as well as acute or chronic administration produce different changes. The site of origin of the EEG studied also influences the changes in EEG under psychotropic drugs. The changes in EEG during chronic administration usually are not constant, and vary during treatment. The authors' own investigations showed that acute administration of chlorpromazine i.v. produces characteristic changes in the EEG in two stages: (1) an increase in voltage, slowing and strengthening of synchronization, and the rhythmic nature of the background; (2) a depressed voltage, with an increase in appearance of slow waves and slowing or disappearance of fast beta waves. These

changes are definitely analogous to the spontaneous process of falling asleep. The study of a large series of phenothiazine derivatives and structurally related compounds showed that they are either stronger or weaker than chlorpromazine in regard to the above two stages, and that these EEG criteria correspond well with the clinical classification of the neuroleptics. Under the effect of psychotropic drugs, a structural change occurs in the organization of cortical activity. From the psychophysiological viewpoint, this mainly concerns the equilibrium and action of every unspecific excitatory and inhibitory influence that is involved in regulation of the degree of vigilance.

Erlangen, Germany

- 2615 Sadanaga, Yoshiaki, (Experimental studies on influences of various kinds of general anesthesia and several promoting drugs on the cerebrospinal fluid pressure.) *Journal of Kumamoto Medical Society*, 37:162-194, 1963.

The following results were obtained on the cerebrospinal fluid pressure, when dogs were placed under the various kinds of general anesthesia. (1) In all cases of anesthesia in which thiamylal sodium, nitrous oxide, nitrous oxide-oxygen-ether, ether, and fluothane were used, the blood pressure, respiration, and fluid pressure were stabilized during the first stage of the third period. (2) As anesthesia weakens and fits such as body motion, trembling, deep breathing and coughing, occur, the fluid pressure will at the same time, change considerably. (3) In cases of deep anesthesia in which ether and fluothane are used, the fluid pressure will rise. (4) Cerebrospinal fluid pressure will rise sharply in cases of hypoacidemia or storage of carbon-monoxide gas. (5) The fluid-pressure rise described in (3) and (4) above can be restored to normal quickly by removing the causes and by giving oxygen.

(No address)

- 2616 Epstein, Stephan. "Masked" photopatch tests. *Journal of Investigative Dermatology*, 41:369-370, 1963.

The coincidence of positive photopatch tests and plain patch tests in some instances of photoallergic dermatitis, notably from phenothiazine derivatives, may be explained by the fact that the

apparent positive patch test may be an unrecognized photopatch test. A test case of a 58-year-old white male orderly who suffered from acute contact dermatitis of the face and hands and who had dispensed liquid chlorpromazine to patients illustrates this point. Repeated photopatch tests and patch tests were performed with chlorpromazine (2%, 0.2%, and 0.02% solutions) on the patient's back, which was not exposed to sunlight. The photopatch and plain patch tests always gave positive reactions, although the latter tests gave less severe reactions and took a longer time to occur. Tests with promazine and promethazine were positive only at the 2% concentration. Apparent positive plain patch tests with chlorpromazine have been shown to be actually "masked" photopatch tests; that is, the patch tests became positive because of unintentional and unsuspected exposure to window filtered light. This explanation may apply to a number of previous reports concerning the coexistence of plain and photo contact sensitivity. In the future, a "blackout" test should be applied in such instances to determine whether the positive plain patch tests truly represent a double sensitivity or are the result of "masked" photoallergy.

Marshfield Clinic Foundation for
Medical Research and Education
Marshfield, Wisconsin

2617 Pujman, V., Černochova, S.,
Hampejsova, H., & Jedlickova, M.
The effect of chlorprothixene and 6-mer-
captopurine on the LA VUFB mouse leukaemia.
Neoplasma, 10(4):365-370, 1963.

The effect of chlorprothixene and 6-mer-
captopurine on the course of LA VUFB mouse
leukemia has been studied in 225 C57 Black
mice weighing 18 to 23 g. They were
transplanted with leukemia by i.p. injection
of leukemic liver. The total doses of each
drug were administered 24 hours after
leukemia injection in six divided doses
over 6 days, and on the seventh day the
animals used for the study of the white
blood cells and weight of organs were
sacrificed; mice for the study of survival
times were followed up to death. Chlor-
prothixene was injected s.c. in total doses
of 6, 12, and 22.5 mg/kg; 6-mercaptopurine
was given orally through a tube in total
doses of 45, 90, and 180 mg/kg. Controls
were injected with solvent only. Higher
total doses of chlorprothixene increased
the survival time of leukemic mice and
decreased the weight of leukemic organs.

The total doses of 6-mercaptopurine alone
and 6 mg/kg of chlorprothixene alone
influenced the course of leukemia insignifi-
cantly. Combination of 6 mg/kg of chlor-
prothixene with doses of 90 and 180 mg/kg of
6-mercaptopurine brought a significant
increase in survival time, a decrease in the
weight of leukemic liver and spleen, and a
drop in the white-cell count in peripheral
blood. Combination of higher doses of both
drugs exerted an antileukemic action, except
the dose of 22.5 mg/kg chlorprothixene
combined with 180 mg/kg of 6-mercaptopurine.
Following this, the body weight of experi-
mental mice dropped, and the survival time,
probably owing to toxic effect, was
shortened.

Research Institute for
Pharmacy and Biochemistry
Prague, Czechoslovakia

2618 Taylor, Russell. Chemical stimulants
to respiration. Applied Therapeutics,
5:1019-1021, 1963.

A general survey of respiratory stimulants
and their mode of action is presented.
The respiratory stimulants are grouped
into two broad clinical classes---CNS
stimulants and modifiers of carbon dioxide
metabolism. Modifiers of CO₂ metabolism
include acetazolamide, dichlorphenamide,
and trihydroxymethylaminomethane. The
CNS stimulants are further classified
according to site of action: cerebral,
brain stem, spinal, and reflex. The
following drugs in these categories are
discussed: (1) cerebral---aminophylline,
caffeine, and theophylline; (2) brain
stem---amiphenazole, camphor, CO₂,
ethamivan, menthol, bemegride, pentylenete-
trazol, picrotoxin, prethcamid, nikethamide,
AHR-619, and DW-62; (3) spinal---strychnine;
and (4) reflex---lobeline and nicotine.

University of Toronto
Toronto, Ontario, Canada

2619 Torra, Aquiles, Marquillo, Carlos L.,
Esperben, Maria T., & Lasalvia, E.
Action of monoamine oxidase inhibitors upon
red cell pyruvate levels. Chemotherapy,
7:93-96, 1963.

The influence of MAO inhibitors (nialamide
and Ro 4-1634) on pyruvate levels in plasma
and red cells was investigated. Two tubes,
each containing 7 ml of red cells, were
used; 1 ml of saline was added to one

tube and 1 ml of saline containing 10 mg of MAO-I was added to the other tube. The tubes were incubated at 37° C. The red cell tubes incubated with the MAO inhibitors showed a marked increase in the pyruvic acid content after 3 hours; after 20 hours, the acid content in both tubes, with or without inhibitors, was the same. There was no change in the pyruvic plasma level.

Department of Clinical and
Laboratory Investigation
Montevideo, Uruguay

2620 Hopkin, D. A. Buxton. **Some recent views on the mechanisms of consciousness and the differences between the central actions of anaesthetics and some of the newer sedative agents.** Proceedings of the Royal Society of Medicine, 56:981-983, 1963.

A review is given of studies that determined the sleep and arousal centers and their pathways in the CNS. The differential effects of anesthetics and other centrally active sedatives on these centers are described. Studies on the distinction between the action of chlorpromazine and thiopental on the reticular activating system and on the differential effects of chlorpromazine and opiates in the CNS are reported.

Charing Cross Hospital Medical School
London, England

2621 University of Washington. **Cardio-vascular response to stress in surgical patients under halothane anesthesia.** Bonica, John J., St. Louis, 1963, 20 p. Contract DA-49-193-MD-2231, unclassified report.

Fifteen unselected patients (22 to 72 years of age) of both sexes scheduled for elective surgery were monitored for cardiac output, total blood volume, blood arterial oxygen pressure (PaO₂), arterial carbon dioxide pressure (PaCO₂), arterial pH (apH), ECG, and continuous arterial and venous pressures before induction of halothane-oxygen anesthesia, after anesthesia but before surgery, and following surgery and anesthesia. Patients were examined after breathing 100% oxygen for 15 minutes, after i.v. injection of atropine or scopolamine (0.4 mg), and then after light halothane anesthesia. After termination of anesthesia,

the patient was given 100% oxygen again for 15 minutes. The average mean arterial pressure was decreased significantly during anesthesia and postoperatively. The cardiac rate was significantly changed only in the postoperative period due to the stress caused by surgery and blood loss. Cardiac output and stroke volume were decreased with deep anesthesia and in the postoperative period, again due to stress of surgery and blood loss. In general, there was a tendency toward CO₂ retention and acidosis in all patients, but this was not significant. Light halothane anesthesia did not depress cardiovascular function to a significant degree, but did cause very mild respiratory depression. The basis of this lack of cardiovascular depression was discussed. Depression occurring with increased duration of anesthesia was also discussed.

University of Washington
St. Louis, Missouri

2622 Nash, Ernest F. & Thomas, Charles E. **Comparative evaluation of hydroxyzine and promethazine in the preanesthetic medication of 500 surgical patients.** Journal of the American Osteopathic Association, 62:1086-1088, 1963.

This study was performed to compare the effectiveness of hydroxyzine and promethazine as preanesthetic medication and to compare the side effects of both drugs; the drugs were administered preoperatively to two matched groups of 250 patients each, selected at random. There were 186 males and 314 females, 10 to 78 years of age. Each group consisted of 93 males and 157 females. The hydroxyzine and promethazine groups corresponded closely in age, weight, and sex. Ninety minutes prior to operation, one group of patients received hydroxyzine (1 mg/lb of body weight), and the second group received promethazine (0.5 mg/lb of body weight). All of the patients received meperidine (0.5 mg/lb) with atropine or scopolamine 45 minutes before the operation. The dosage range for all patients was hydroxyzine (65 to 200 mg), promethazine (25 to 100 mg), meperidine (25 to 125 mg), atropine (0.2 to 0.9 mg), and scopolamine (0.1 to 0.8 mg). The average dosages for the hydroxyzine group were hydroxyzine (138.8 mg), meperidine (74.1 mg), atropine (0.41 mg), and scopolamine (0.34 mg). The average dosages for the promethazine group were promethazine (65.7 mg), meperidine (70.3 mg), atropine (0.39 mg), and scopolamine (0.30 mg). The preoperative blood pressure results were the same in both groups. There was no significant difference

in the psychic states of both groups prior to anesthesia. The preoperative sedation effect was almost identical in both groups. Side effects were noted in both groups—restlessness (60 of the promethazine group and 33 of the hydroxyzine group), hypotension, vomiting and emergence delirium. The clinical study showed that hydroxyzine is more applicable than promethazine as an adjunctive in preoperative medication.

Detroit Osteopathic Hospital
12523 Third Avenue
Detroit, Michigan

- 2623 Gioldanowski, Jerzy. **The influence of drugs with various permeability through the vasculo-cerebral barrier on the microphonic potential of the organ of Corti. II. Levels of the drugs in the cerebrospinal fluid.** *Archivum Immunologiae et Therapiae Experimentalis*, 11:471-477, 1963.

To determine the degree of penetration of various drugs through the blood-brain barrier, experiments were performed in cats (1.80 to 3.50 kg in weight) under urethane anesthesia in which the microphonic potential of the organ of Corti was recorded simultaneously with the concentration of the drugs in the cerebrospinal fluid. The drugs were injected i.v. or s.c. The drugs were phenergan (1 mg/kg), multergan (1 mg/kg), sulfapyridine (100 mg/kg), *N*-oxide of sulphapyridine (100 mg/kg), napharsen (2 mg/kg), acetarsol (20 mg/kg), and pentothal (5 mg/kg). The ability of drugs to pass through the blood-brain barrier is correlated only to a limited extent with their action on the microphonic potential. Permeation of drugs into the labyrinthine fluids does not necessarily accompany their permeation into the cerebrospinal fluid. In the case of some compounds (e.g., the sulphonamides), however, ability to penetrate both barriers may be similar.

School of Medicine
Wroclaw, Poland

- 2624 Waitzman, Morton B. **Influences of chlorpromazine on aqueous humor dynamics.** *Acta Ophthalmologica*, 41:1-8, 1963.

The intraocular pressure (IOP) and aqueous-flow effects of chlorpromazine and the usefulness of this drug in reducing, to a minimum, excitement-related influences of animal manipulation on tonography were

investigated. The experimental animals (male albino rabbits, weighing 4 to 6 pounds) were given a 1% solution of chlorpromazine (1 mg/kg) 2 to 4 hours prior to tonography by deep i.m. hindlimb injection. The animals were handled in such a way as to reduce a minimum trauma that might affect tonographic effects adversely. This method is suggested as a routine procedure to reduce to a minimum undesirable variance and trauma-associated errors in the measurements. A tonographic evaluation on a group of animals, particularly if undramatic results are anticipated, cannot be done in one day, but may be done repetitively on a semiweekly basis.

Laboratory for Ophthalmic Research
Emory University
School of Medicine
Atlanta, Georgia

- 2625 Harvard Medical School. **Catecholamine release from adrenal slices and rate of respiration.** Technical report, Draskóczy, P. R., Burack, W. R., & Weiner, N., Boston, Massachusetts, September 1963, 8 p. Contract AF 41(657)-414, unclassified report.

The influence of potassium ion, 2,4-dinitrophenol (DNP), tyramine, and reserpine on catecholamine release from and oxygen consumption of the adrenal slices from fowl is investigated. In each experiment, the right and left glands of the same animals were compared, one serving as the control and the other as the experimental sample. The gland to be exposed to one of the agents under study was selected at random. At 37° C, about 50% of the original catecholamine content remained in the slices after 7 hours of incubation. At 4° C, the rate of depletion was much lower; more than 90% of the original catecholamine content was still present in the slices after 7 hours. Potassium ion, added to the medium as KCl (0.1 M), and tyramine 7.3×10^{-3} M did not influence the oxidative metabolism, but had a definite effect on the catecholamines release. During the first 30 minutes of incubation, catecholamine release was 37% greater for slices exposed to excess KCl than for control slices, and the increase in catecholamine release with tyramine was significant after 2 hours of incubation. Reserpine (3.3×10^{-5} M) depressed the oxygen consumption but had no effect on the rate of catecholamine release. The DNP (7×10^{-5} M) produced a marked increase in oxygen consumption (37.5% higher than controls) but did not increase the catecholamine release during the first 2 hours of

incubation. However, after 5 hours, the rate of release was increased. None of the four agents produced an increase in the amount of protein released.

Department of Pharmacology
Harvard Medical School
Boston, Massachusetts

2626 Riffi, G. F. & Zamparo, L. *Effetti dell'atropina sull-EEG e sul condizionamento della scimmia. (Effects of atropine on the EEG and conditioning in the monkey.)* Archivio Italiano di Scienze Farmacologiche, 13(3):3-4, 1963.

Experiments were performed to verify previous reports that the classical EEG picture produced by atropine (slowing of cortical activity and disappearance of the arrest reaction to external stimuli) was not accompanied by behavioral changes. Classical conditioning techniques were used, which provided a more exact means than simple observation of evaluating behavior. Four monkeys were trained to respond to noise and light stimuli. Atropine was given s.c. 1 hour before each experiment. In contrast to previous findings, alterations in the EEG produced by atropine were accompanied by changes in behavior. The results confirm the hypothesis that atropine (and other anticholinergic drugs) exert a measurable effect on attention and the learning process.

Institute of Pharmacology
University of Pisa
Pisa, Italy

2627 Kuriyama, H. *Electrophysiological observations on the motor innervation of the smooth muscle cells in the guinea-pig vas deferens.* Journal of Physiology, 169:213-228, 1963.

These studies were carried out in an attempt to clarify the nervous pathway and the site of action of ganglion-blocking and adrenergic blocking agents on the hypogastric nerve of the guinea-pig vas deferens. The Hukovic, Burnstock, and Holman method was used for the nerve preparation. The amplitude of the junction potentials that were recorded from the muscle cells varied according to the frequency, intensity, and duration of the stimulus. The neuromuscular junction potentials, action potentials, and tension evoked by nerve stimulation and field stimulation of the muscle

were recorded from single cells in the hypogastric nerve preparation. The junction potentials elicited by short pulses (0.01 msec) with either nerve or field stimulation were qualitatively alike, but not always of the same amplitude. The findings suggested a multiple innervation of individual muscle cells and a variable degree of overlap. The conduction velocity of the nerve fiber was measured from the latency of the junction potential at 10 mm intervals along the nerve trunk. The velocity varied from 0.7 to 2.8 m/sec along the last 10 to 20 mm of the nerve trunk, but there was considerable delay at the point where the nerve entered the muscle. Nicotine HCl (10^{-5}) blocked the generation of junction potentials in response to nerve stimulation (0.01 msec), but had no effect on those evoked by field stimulation. Hexamethonium bromide (10^{-4}) produced the same effect. The tension response elicited by short pulses to the nerve was abolished, whereas the tension attributable to long pulses remained constant in the presence of these agents. Ganglion-blocking agents did not block the generation of junction potentials nor the tension produced by field stimulation. Bretylium (10^{-6}) and phentolamine 3×10^{-5} g/ml abolished the generation of junction potentials for both types of stimulation.

Department of Pharmacology
University of Oxford
Oxford, England

2628 Gyls, J. A., Muccia, P. M. R., & Taylor, M. K. *Pharmacological and toxicological properties of 2-methyl-3-piperidinopyrazine, a new antidepressant.* Annals of the New York Academy of Sciences, 107:899-913, 1963.

The purpose of this work is to present the pyrazine compounds as a new class of MAO inhibitors and to compare 2-methyl-3-piperidinopyrazine HCl (W 3207A) with other known antidepressants. The following experiments were performed: reserpine reversal test in mice, potentiation of biogenic amines (5HTP, *DL*-DOPA, or tryptamine) in mice, reversal of reserpine effects of pentylenetetrazol and maximal EST seizures in mice; antagonism of reserpine hypothermia in mice; tetrabenazine reversal in rats; cardiovascular studies in the anesthetized dog; acute-toxicity studies in mice, rats, and dogs; and subacute-toxicity studies in dogs and rats. The pyrazine compounds were active in the reversal test measuring brain MAO inhibition in vivo.

A tertiary amino group (cyclic or acyclic) in the adjacent position to the alkyl moiety on the pyrazine ring was required for the activity. The W 3207A reversed reserpine depression, potentiated CNS effects of biogenic amines, and exhibited a wide separation (fiftyfold to one hundredfold) between effective and lethal doses in mice. In this respect, W 3207A compared favorably with phenelzine, isocarboxazid, and tranylcypromine. The activity of W 3207A in the reserpine reversal test persisted for at least 7 days. The W 3207A was four to six times more potent than phenelzine in antagonizing reserpine facilitation of convulsions induced by pentylenetetrazol or maximal EST. In reversal of reserpine hypothermia, W 3207A was equipotent to imipramine, and phenelzine was considerably weaker. Differences in the gross behavior patterns of W 3207A and phenelzine, as compared to imipramine, were shown in the tetrabenazine reversal test in rats. The W 3207A increased arterial pressure and cardiac contractile force in 3 hours, with little effect on right atrial pressure, ECG, and heart rate in the anesthetized dog. The W 3207A potentiated pressor responses of phenethylamine and dopamine and reversed reserpine effects on blood pressure. The W 3207A had a low oral acute toxicity in rats and mice, but the toxicity that occurred when using parenteral routes were markedly increased. Toxicity of W 3207A significantly increased with the age of rats. Dogs exhibited a higher susceptibility to W 3207A than mice or rats. Pretreatment with W 3207A increased the sleeping time of hexobarbital-treated mice and acute toxicity of imipramine in mice. The W 3207A did not produce any hematological and histopathological changes in dogs and rats that were dosed chronically for 8 to 10 weeks, respectively.

Warner-Lambert Research Institute
Morris Plains, New Jersey

2629 Dubnick, Bernard, Morgan, D. Fay, & Phillips, George E. **Inhibition of monoamine oxidase by 2-methyl-3-piperidinopyrazine.** *Annals of the New York Academy of Sciences*, 107:914-923, 1963.

The MAO-inhibitory activity has been discovered in a new series of compounds of which 2-methyl-3-piperidinopyrazine (W 3207A) is a representative member. The MAO inhibition after a single dose of W 3207A (50 mg/kg i.p.) was rapid in onset (complete within 15 minutes) and of long duration (demonstrable for weeks) in the mouse brain

and liver. The W 3207A may occupy the same site on MAO as do harmaline, the hydrazines, and serotonin. Harmaline and serotonin antagonized W 3207A to a degree that was directly proportional to the ratio of doses. The W 3207A (40 mg/kg i.p.) also inhibited diamineoxidase (10^{-3} M) in guinea-pig liver or rat intestine. Evidence that W 3207A requires biotransformation before showing MAO-inhibitory activity was found when the rather low potency of the compound (10^{-3} required to produce 50% inhibition) in vitro was observed.

Warner Lambert Research Institute
Morris Plains, New Jersey

2630 Kuntzman, Ronald & Jacobson, Martin M. **The inhibition of monoamine oxidase by benzyl and phenethylguanidines related to bretylium and guanethidine.** *Annals of the New York Academy of Sciences*, 107:945-950, 1963.

This report demonstrates that benzylguanidine and phenethylguanidine are competitive and reversible inhibitors of MAO in vitro and in vivo and that *N*-*O*-chlorobenzyl-*N'*, *N''*-dimethylguanidine (BW 392 C60) is just as potent an inhibitor in vitro as phenylisopropylhydrazine (PIH), whereas its dechlorinated analog, *N*-benzyl-*N'*, *N''*-dimethylguanidine (BW 467 C60, bethanidine) has little activity. The significance of these data in the lowering of blood pressure by guanidines is discussed. The experiments performed were: inhibition of rat-heart MAO activity in vitro by a series of guanidines (5×10^{-4} , 10^{-5} , and 10^{-6} M); effects of preincubation time and dialysis on the inhibition of MAO activity in vitro produced by BW 392 C60 and PIH; the competitive nature of MAO inhibition in vitro by BW 392 C60; in vivo inhibition of MAO by BW 392 C60 (3 and 50 mg/kg) and bethanidine (50 mg/kg) (the formation of 5HIAA from exogenously administered 5HT was used as an assay of MAO activity in mice); and the effect of BW 392 C60 in the inhibition of MAO produced by PIH.

Burroughs Wellcome & Co., Inc.
Tuckahoe, New York

2631 Schildkraut, Joseph J., Klerman, Gerald L., Friend, Dale G., & Greenblatt, Milton. Biochemical and pressor effects of oral D,L-dihydroxyphenylalanine in patients pretreated with antidepressant drugs. *Annals of the New York Academy of Sciences*, 107:1005-1015, 1963.

Changes in the level of plasma catecholamines and associated changes in blood pressure following oral D,L-DOPA were measured under the following pharmacological conditions: (1) placebo control, two patients; (2) phenelzine pretreatment (45 to 60 mg/day for 3 weeks), three patients; and (3) imipramine pretreatment (100 to 150 mg/day for 3 weeks), one patient. Blood pressure was measured immediately before and every 10 minutes for 2 hours after DOPA administration. Blood samples were drawn before and 1, 2, and 4 hours after DOPA. The DOPA caused a twofold to threefold elevation in plasma catecholamines in patients taking phenelzine. A pressor response with accompanying bradycardia was seen in two of the three subjects. A similar elevation in catecholamines was seen in the imipramine patient, but no pressor response occurred. No elevation in catecholamines was seen in placebo patients. These findings are discussed in the light of reports by other investigators of the potentiation of the pressor effects of DOPA and the catecholamines by MAO inhibitors, and of the inhibition of tissue uptake of catecholamines by imipramine. The relationship of the elevation of plasma catecholamines to the pressor response is considered.

Harvard Medical School
Boston, Massachusetts

2632 Garattini, S. & Valzelli, L. Biochemistry and pharmacology of serotonin in the central nervous system. In: de Ajuriaguerra, J., ed. *Monoamines et système nerveux central. (Monoamines and the central nervous system.)* Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 59-88.

A review of the knowledge on the biochemistry of serotonin (5HT) in the brain included a discussion of drugs interfering with enzymes involved in 5HT synthesis and inactivation as well as drugs that release 5HT from its binding sites. There is a major difficulty in evaluating the role of 5HT in the CNS due to impermeability of the brain to the amine. The MAO is the main metabolizer of 5HT that exists in a bound form in the brain. The

half-life, measured as the time required to increase brain 5HT by 50% ($0.235\mu\text{g/g}$), is calculated to be about 12.5 minutes. A study of the relationship between the biochemical effects and the pharmacological activities of reserpine has shown that three major pharmacological activities of reserpine (hypotension, sedation, and pituitary stimulation) may be related to the changes of the amines in the brain. Three groups of drugs that antagonize the central symptomatology of reserpine (central stimulants, MAO inhibitors, and imipramine-like compounds) may have important implications insofar as the mechanism of human depression is concerned. Agents that show antiserotonin activity (LSI and chlorpromazine) should also show anti-reserpine activity. Since these compounds do not, the question arises as to whether these results are conclusive. It was concluded that the knowledge on 5HT in the brain is limited and contradictory and that the field needs further investigation.

University of Milan
Milan, Italy

2633 Pletscher, A. & Gey, K. F. Drug-induced alterations of the metabolism of cerebral monoamines. In: de Ajuriaguerra, J., ed. *Monoamines et système nerveux central. (Monoamines and the central nervous system.)* Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 101-115.

The action of psychotropic drugs on the cerebral monoamine metabolism is discussed. The drugs are classified into four categories according to their presumable mechanism of action: (1) decrease of storage capacity of tissues for monoamines—long-acting Rauwolfia alkaloids and short-acting benzquinolizine derivatives; (2) inhibition of synthesis of monoamines—decarboxylase inhibitors; (3) inhibition of monoamine metabolism—long-acting MAO inhibitors and inhibitors of O-methyl-transferase; (4) interference with monoamine penetration—phenothiazines and thioxanthenes. Groups 1 and 2 cause a decrease of monoamines in the brain. Group 3 causes an increase in cerebral monoamines. Group 4 possibly inhibits the penetration of monoamines to the receptor sites.

Medical Research Department of
F. Hoffman-La Roche & Company Ltd.,
Basel, Switzerland

2634 Tissot, R. *Connaissances expérimentales sur les monoamines et quelques syndromes psychiatriques.* (Experimental information on monoamines and some psychiatric syndromes.)

In: de Ajuriaguerra, J., ed. *Monoamines et système nerveux central.* (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 169-207.

The possible role of monoamine metabolism imbalance in the development of certain psychiatric syndromes is discussed, and two series of experiments pertaining to this possible relationship are described. The hypothesis that one or more disturbances in monoamine metabolism are present in depressive and manic-agitation syndromes is supported by clinical evidence reported in the literature; monoamine metabolism imbalance does not appear to have a part in hebephrenic—catatonic or schizophrenic syndromes. The results of experiments on the urinary excretion of 5HIAA in 106 patients, all but 27 of whom had syndromes of depression or excitation with manic characteristics, are reported. The effect of MAO inhibitors on depressed patients with initial 5HIAA excretion levels above normal is discussed. Results indicate that the greater the initial excretion of 5HIAA, the better the chances are that a depressed patient will respond to MAO inhibitors. (74 references)

Psychiatric Clinic
University of Geneva
Bel-Air, Geneva, Switzerland

See also: 2478, 2502, 2533, 2544, 2640, 2653

BIOCHEMISTRY

2635 Allgén, L.-G., Hellström, Lajla, & Sant'Orp, C. J. On the metabolism and elimination of the psychotropic phenothiazine drug levomepromazine (Nozinan) in man. *Acta Psychiatrica Scandinavica*, Supplement 169:366-381, 1963.

Methods are described for determining the presence of levomepromazine in the urine and serum of patients who are taking the drug. The elimination of levomepromazine sulfoxide and of levomepromazine in the urine of 17 patients (21 to 57 years of age) receiving 100 to 450 mg/day of levomepromazine in divided doses is discussed. Most of the patients were schizophrenic. The average excretion of levomepromazine sulfoxide in the urine was 10.1% of the daily dose. About 1% of the daily dose of nonoxidized drug appeared in the urine. No sulfoxide was found in the feces, but the elimination of apparent drug in feces is highly variable, depending upon the feces volume. A maximum value of 14% of the daily dose was found (with feces volume of 500 ml). Glucuronic acid conjugates were eliminated in the urine, but not in the feces. In two patients given an oral dose of 400 mg/day of the drug, the serum analyzed for apparent drug and sulfoxide was less than 0.1 mg percent. One schizophrenic patient who received levomepromazine 50 to 150 mg i.m. b.i.d. or t.i.d. showed an increase in the elimination of sulfoxide after the first 24 hours (up to 11% of the dose). When the dose level is increased, the percent elimination of sulfoxide decreases again. The elimination of apparent levomepromazine in urine is low. Other metabolites are discussed.

Department of Clinical Chemistry
Beckomberga Hospital
Bromma, Sweden

2636 Martin, H. F., Price, Steven, & Gudzinowicz, B. J. Evidence for the complexing of oxygen by phenothiazines. *Archives of Biochemistry and Biophysics*, 103:196-199, 1963.

The effect of several phenothiazines (promethazine, thioridazine, promazine, chlorpromazine, trifluorpromazine, and chlorpromazine and methoxypropazine) on oxygen reduction potentials was studied polarographically. The polarographic solutions consisted of aqueous 0.1 M potassium chloride with 5 to 20 mg of the phenothiazine added. For each compound, at least three polarograms were determined: (a) an air-saturated solution showing the conversion of oxygen to hydrogen peroxide; (b) the same solution, after adding the indicated phenothiazine; and (c) the same solution after bubbling with nitrogen for 15 minutes. Phenothiazine derivatives were found to "shift" the first oxygen reduction potential with E_1 volts. Degassing with nitrogen always resulted in disappearance of the waves. Oxygen bubbled through degassed solutions resulted in nearly perfect reproduction of the shifted oxygen curve seen in phenothiazine-containing solutions prior to degassing. Identical curves were obtained, whether scanning from positive to negative or from negative to positive potentials. There was an apparent correlation between the reduction potential of the phenothiazine solutions in the presence of oxygen and the oxidation potentials of the various 2-substituted phenothiazines. Correlations of the differences between the oxygen reduction potential and those of the complexes with the spectra and Hammett δp values of the phenothiazines suggest that σ , rather than π , complexes are probably involved. On the basis of their reduction potentials, the oxygen--phenothiazine drug complexes are poorer oxidizing agents than oxygen, by several orders of magnitude.

Monsanto Research Corporation
Boston Laboratories
Everett, Massachusetts

- 2637 U.S. Army. Preliminary design report. Lysergic acid derivatives program. Part I. - Process details. Dickey, George F. Edgewood Arsenal, Maryland, Chemical Research and Development Laboratories, 1963, 33 p.

This report describes equipment and instrumentation required to start up and operate a small batch fermentor for producing lysergic acid derivatives (LAD). The length of time required to produce the maximum yield of LAD is estimated at approximately nine days. A description of the media constituents used in fermentation is presented. A time schedule and cost estimate of the development program proposed is given.

Directorate of Weapons Systems
U.S. Army
Chemical Research and
Development Laboratories
Edgewood Arsenal, Maryland

- 2638 Tsukamoto, Hisao, Yoshimura, Hidetoshi, & Tatsumi, Kiyoshi. Metabolism of drugs. XXXV. Metabolic fate of meprobamate. (3). A new metabolic pathway of carbamate group—the formation of meprobamate N-glucuronide in animal body. Chemical and Pharmaceutical Bulletin, 11(4):421-426, 1963.

The structure of meprobamate-N-glucuronide, one of the principal metabolites of meprobamate, has been established. Meprobamate (0.25 g/kg body weight) was administered to 20 rabbits, and the 24-hour urines were collected and extracted. Paper chromatography and the infrared spectrum showed the metabolite to be meprobamate-N-mono- β -D glucopyranosiduronic acid, which was synthesized for comparison, by direct condensation of meprobamate and glucuronic acid. By isolating the glucuronide from the reaction mixture of 0.1 g meprobamate and 0.5 glucuronic acid in 200 cc of normal rabbit urine that was allowed to stand at room temperature for 10 days, it was proved that the glucuronide was not formed spontaneously during the course of extraction, but only by the enzyme system in the animal body.

Kyushu University
Katakasu, Fukuoka, Japan

- 2639 Forrest, Fred M. & Forrest, Irene S. Urine testing for phenothiazine and related drugs. Its significance for achieving and maintaining rehabilitation of chronic mental patients. American Archives of Rehabilitation Therapy, 11(1):8-19, 1963.

The results of treatment with phenothiazine drugs in more than 1,000 chronic mental patients were reported, and the significance of checking the patients for continued drug intake by using the FPN urine tests was discussed. Over 50% of the patients were drug rehabilitated and discharged, and about 25% of these relapsed due to reduced drug dosage or withdrawal of medication. The great majority of patients who remained well were taking maintenance doses of 600 to 1,200 mg of chlorpromazine or equivalent doses of other phenothiazine drugs. It was concluded that in order to keep drug-maintained, chronic mental patients functioning in the community, the persistent high dosages on which the patient recovered should be prescribed at monthly intervals and urine tests made in order to ascertain that the drug is being taken.

V. A. Hospital
Palo Alto, California

- 2640 Magee, W. L., Berry, J. F., Strickland, K. P., & Rossiter, R. J. Labelling of phospholipids from inorganic [^{32} P]phosphate in brain preparations. Effect of acetylcholine, chlorpromazine and azacyclonol. Biochemical Journal, 88:45-52, 1963.

The increase in the labeling in vitro of phospholipids brought about by the addition of two compounds that possess tranquilizing properties, chlorpromazine and azacyclonol, was investigated in guinea-pig brain slices, dispersion and mitochondrial preparations from rat brains, and liver and in kidney and pancreas guinea-pig tissue. The addition of chlorpromazine (0.1 mM) or azacyclonol (1 mM) increased the incorporation of inorganic [^{32} P] phosphate into the phospholipids of slices of the guinea-pig brain without any increase in the consumption of oxygen, production of lactic acid, concentration and specific radioactivity of adenosine triphosphate, or concentration of phosphocreatine. The increase in labeling was confined to phosphatidic acid, phosphatidylinositol, and phosphatidylserine. In the dispersion preparation of the rat brain, neither compound caused an increase in the labeling of phospholipid, but there was a small increase in the labeling of phospholipid in the

mitochondrial preparations at the same concentrations as in guinea-pig brain. Chlorpromazine (0.1 mM) was without effect on liver, kidney, and pancreas tissue, whereas azacyclonol (1.0 mM) caused an increase in the labeling of phospholipids in each of the four tissues. Higher concentrations of chlorpromazine (1 mM) and azacyclonol (5 mM) in each of the tissues studied caused a decrease in the labeling of phospholipids, accompanied by a reduction in oxygen consumption, in concentration and specific radioactivity of arenosine triphosphate, and in concentration of phosphocreatine. Chlorpromazine (0.1 mM) had a negligible effect on cholinesterase activity, whereas physostigmine (0.1 mM) almost completely inhibited cholinesterase activity, but had no effect on phospholipid labeling.

University of Western Ontario
London, Canada

2641 Leusen, I. Actions neurophysiologiques des mobilisateurs des monoamines et des inhibiteurs de la monoamine-oxydase. (Neurophysiological action of monoamine mobilizers and monoamine oxidase inhibitors.) In: de Ajuriaguerra, J., ed. Monoamines et système nerveux central. (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 119-131.

Studies on the role of monoamines in the functioning of the nervous system in general, and of the CNS in particular may be divided into two groups: research on the modification of monoamine concentration, particularly an increase based on monoamines and their precursors; and modification of monoamine concentration at the CNS level by monoamine mobilizers and MAO inhibitors. For example, reserpine has a striking sedative effect on the CNS, causing a disequilibrium of the CNS components. Benzoquinolisine derivatives, such as tetrabenzine, produce nervous effects and lower the cerebral monoamine concentration. Many experiments show that MAO inhibitors increase the concentrations of certain monoamines at the CNS level. However, the correlation between monoamine concentration and MAO inhibitors influences the metabolism of monoamines and also inhibits other enzyme activity. In effect, MAO inhibitors have a polyvalent action, depending on subject, dose, and condition.

Laboratory of Physiopathology
University of Ghent
Ghent, Belgium

2642 Dell, P. Monoamines et systèmes de projections diffuses. (Monoamines and diffuse projection systems.) In: de Ajuriaguerra, J., ed. Monoamines et système nerveux central. (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 133-142.

Adrenaline cortical arousal levels support the argument for the existence of adrenergic mechanisms at the reticular level. It has been shown that adrenaline affects the ascending reticular activator system. Anterior portions of the cerebral trunk injected with adrenaline show a strong electrocortical response, lasting 2 or 3 minutes; on the other hand, adrenaline cortical arousal is not evident in the posterior portions of the cerebral trunk after destruction of the mesencephalic reticular formations by coagulation. Data show that the bulbar reticular structures depress the cortical effects of the mesencephalic reticularization by inhibiting the reticular activator discharges, causing deactivation. Thus, this counter-regulatory mechanism either decreases or suppresses the adrenaline level. Adrenaline also affects the descending reticular system. A reticular-cortical-reticular circuit with a negative feedback adjusts the level of reticular activation.

Neurophysiology Laboratory
Henri Rousselle Hospital
Paris, France

2643 Carlsson, Arvid & Lindqvist, Margit. DOPA analogues as tools for the study of dopamine and noradrenaline in brain. In: de Ajuriaguerra, J., ed. Monoamines et système nerveux central. (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 89-92.

The modes of action of α -methyl-3,4-dihydrophenylalanine (α -methyldopa) and α -methyl-tyrosine were investigated in order to determine whether these drugs might be useful tools in clarifying the physiological mechanisms of brain monoamines. When the levels of α -methyldopa, noradrenaline, dopamine, and 5HT in the brains of mice injected with α -methyldopa were investigated, it was found that the amino acid caused a slight and transient drop in 5HT and dopamine, a marked and long-lasting depletion of noradrenaline and that α -methyldopa disappeared from the brain at a much slower rate than DOPA. From this result it seemed that the action of

α -methyldopa was not a direct one; therefore, the metabolites of α -methyldopa were investigated. The decarboxylation product of α -methyldopa, α -methyldopamine, was found to appear in the brains of mice at a level of 0.5 μ g/g to 1 μ g/g within one-half hour after injection of α -methyldopa (400 mg/kg i.p.). The levels of α -methyldopamine in the brains of rabbits after injection of α -methyldopa (200 mg/kg i.v.) were found to be much higher in the striatum and in the brain stem than in the cerebellum and the hemispheres. Since the depletion of noradrenaline persisted for at least 12 hours after the injection when α -methyldopamine was no longer detectable, it seemed that the disappearance of noradrenaline was due to displacement by α -methyl-noradrenaline, the hydroxylation product of α -methyldopamine.

University of Göteborg
Göteborg, Sweden

2644 Waelsch, Heinrich. The amine incorporating system (transglutaminase). In: de Ajuriaguerra, J., ed. Monoamines et Système nerveux central. (Monoamines and the central nervous system.) Symposium Bel-Air, Genève, September 1961. Paris, Masson, 1962, p. 93-104.

Studies on the amine incorporating activity of several amines in various substrates are discussed; the studies showed that transglutaminase may catalyze the replacement processes of the amide group of protein-bound glutamine by a primary amine or ammonia. This primary amine may be added to the reaction mixture, and in its absence, the epsilon-amino group of protein-bound lysine may be added. The enzyme catalyzes the hydrolysis of the amide group of protein-bound glutamine. Pertussis vaccine and a variety of endotoxins increased the activity of transglutaminase in mouse liver, spleen, and lung. The histamine content was determined in liver proteins of normal and endotoxin-treated animals with and without administration of histamine (37.5 mg/kg) prior to sacrifice. The histamine content of proteins was not detectable. When histamine was administered to endotoxin-treated mice, a significant increase of protein-bound histamine was found. This correlates well with the enzyme increase.

New York Psychiatric Institute
New York, New York

2645 Fuxe, Kjell. Cellular localization of monoamines in the median eminence and in the infundibular stem of some mammals. *Acta Physiologica Scandinavica*, 58:383-384, 1963.

The purpose of this investigation was to determine the cellular localization of monoamines in the median eminence and in the infundibular stem of some mammals, and to study the relation of the amines to the portal system. The determination was done by the histochemical fluorescence method. In the cat and guinea pig, fluorescent material was observed to be localized within five nerve fibers that are concentrated in the superficial zone, surrounding the primary capillary plexus, which is drained into the portal vessels. This fluorescence disappeared in the rat after 0.5 mg/kg of reserpine and in rats and mice after 400 mg/kg i.p. of *m*-tyrosine. It would seem that the fluorescent material is derived from primary catecholamines and that dopamine may be the chief amine in the fluorescent nerve fibers surrounding the primary capillary plexus. These results indicate that these catecholamines act as neurohumoral transmitters for the regulation of the activity of the anterior pituitary.

Karolinska Institute
Stockholm, Sweden

2646 von Euler, U. S. & Lishajko, F. Catecholamine release and uptake in isolated adrenergic nerve granules. *Acta Physiologica Scandinavica*, 57:468-480, 1963.

Granules obtained from bovine splenic nerves were investigated for their uptake of exogenous noradrenaline, and the specificity of this uptake was studied by exposing the granules to adrenaline. The isolated storage granules incubated in neutral isotonic potassium phosphate gave off noradrenaline at rates rapidly increasing with the temperature. Noradrenaline (10 μ g/ml to 20 μ g/ml) in the incubation fluid prevented the release of noradrenaline for as long as 2 hours. The noradrenaline was then released at the normal rate after removal of the amine from the incubation fluid. After depletion, the granules were able to take up noradrenaline and adrenaline to about the original content when exposed to the catecholamines (10 μ g/ml to 20 μ g/ml). This suggested a limited storage capacity of the granules. A small net increase of the sum of the amines over the original

amount of noradrenaline suggested that the amines compete for the available binding sites.

Karolinska Institute
Stockholm, Sweden

- 2647 Häggendal, Jan. The presence of 3-O-methylated noradrenaline (normetanephrine) in normal brain tissue. *Acta Physiologica Scandinavica*, 59:261-268, 1963.

The 3-O-methylated noradrenaline (normetanephrine) level in the normal brain tissue of man, pig, and rabbit was investigated, and the effects of certain drugs on this level were studied in order to demonstrate a metabolic pathway for noradrenaline. A combination of column chromatography and spectrophotofluorometry was used for the determination. Normetanephrine was found in the hypothalamus of man (0.04 µg/g to 0.24 µg/g), pig (0.18 µg/g), and rabbit (0.04 µg/g). After reserpine (0.2 mg/kg s.c.), the normetanephrine level in the rabbit was greatly reduced, and 2-(3,4-dihydroxyphenyl)-hexanoylamide (50 mg/kg i.v. for 45 minutes) reduced the normetanephrine level to less than 10% of the normal value. In brain tissue extracts to which normetanephrine (2.5 µg), noradrenaline (2.5 µg), and dopamine (5.0 µg) had been added, normetanephrine (85%), noradrenaline (82%), and dopamine (61%) were recovered. It was suggested that monoamine oxidase regulates the intracellular store of noradrenaline, whereas O-methyltransferase takes part in the metabolism of the active extracellular noradrenaline.

University of Göteborg
Göteborg, Sweden

- 2648 Sanner, Erland. Studies on the excretion mechanism of serotonin (5-hydroxytryptamine) in the chicken kidney. *Acta Physiologica Scandinavica*, 58:330-341, 1963.

The transport mechanism of serotonin was studied in the kidneys of Rhode Island Red chickens (2 years old, 2.0 to 3.5 kg in weight) injected with 10 mg/kg i.v. of 1-phenyl-2-hydrazinopropane (JB-516) at least 1 to 2 hours before the start of the experiment. The transport of serotonin (150 µg to 200 µg), injected into the leg vein of the chicken together with phenol red (800 µg) and tolazoline (5 to 15 mg), was almost completely inhibited. Both

serotonin and phenol red transport were inhibited with tolazoline (50 mg/kg) given 1 hour before serotonin into the wing vein. Probenecid (50 mg/kg) given into the wing vein 1 hour before serotonin--phenol red injections gave a strong inhibition of phenol red excretion but left the serotonin excretion unchanged. Brom cresol green (1 mg) given into the leg vein together with serotonin and phenol red caused inhibition of phenol red transport but left serotonin transport unchanged. Cyanine dye #863, given into the leg vein just before serotonin--phenol red at a dose of 1 mg, gave a small inhibition of serotonin transport, whereas 2 mg inhibited phenol red excretion as well. Reserpine (2.5 to 7.5 mg) did not inhibit either serotonin or phenol red transport. The pH of the urine was increased from 5.5 (normal urine) to 8.0 by addition of isotonic bicarbonate. The pH of the chicken urine did not influence the excretion of serotonin. It was concluded that serotonin is transported in the chicken tubule by the organic base system.

University of Uppsala
Uppsala, Sweden

- 2649 Matsumoto, J. & Nishi, H. Functional mechanism of catechol in the central nervous system. I. The anatomic site of action. *Medical Journal of Osaka University*, 13(4):365-373, 1963.

Three experiments on the functional mechanism of the convulsant catechol in the CNS are reported: (1) the effect of various drugs on catechol-induced convulsions in rats and rabbits; (2) phylogenetic studies of catechol convulsions (in fish, frogs, tortoises, birds, and rats); and (3) analysis of EEG changes induced by catechol and DOPA in rats and rabbits. Catechol convulsions were augmented by noradrenaline, adrenaline, thiopental, and chlorpromazine. Pentobarbital completely suppressed the convulsions, and ether and mephenesin partially suppressed the convulsions. Amobarbital, trimethadione, diphenylhydantoin, pyridoxamine, GABOB, and acetylcholine had no effect. From these findings, catechol appeared to be a different type of convulsant than pentylenetetrazol, strychnine, caffeine, and picrotoxin. Results of the convulsive dose of 50% determined in the phylogenetic studies showed that the sensitivity to catechol was higher in the phylogenetically lower animals. The CD_{50} 's and LD_{50} 's are listed. A subconvulsive dose of catechol increased the fast components in the EEG of the globus

pallidus in contrast to DOPA, which decreased these components. The site of action of catechol appeared to be the globus pallidus.

Osaka University Medical School
Osaka, Japan

2650 Eagleson, D. Allan. Paper chromatographic differentiation of some important phenothiazines encountered in toxicology. Technical Bulletin of the Registry of Medical Technologists, 33(5):78-81, 1963.

A chromatographic method is described for the differentiation and identification of phenothiazine derivatives by measuring R_f values. The method is suggested as an adjunct to existing chemical and instrumental procedures and not as a single criterion for identifying these compounds. The R_f values are listed for chlorpromazine, promazine, trifluorpromazine, prochlorperazine, trifluoperazine, thiopropazate, mepazine, and perphenazine in butanol:HCl:water, butanol:acetic acid:water, and isobutyl alcohol:propionic acid:water systems.

Walla General Hospital
Walla, Washington

2651 Shulgin, A. T. Psychotomimetic agents related to mescaline. Experientia, 19(3):127-128, 1963.

Eight of the higher homologs of mescaline were prepared by reduction of the corresponding nitrostyrenes. A description of the preparation of one nitrostyrene is given. The melting point and yield of the compounds and nitrostyrenes and phenethylamines are given in tabular form. Toxicity and behavioral studies with mice could not distinguish the first three compounds of the series. For all of the compounds, the LD_{50} 's were between 200 and 300 mg/kg i.p.; at 80 mg/kg, there was mild, agitated behavior, with complete recovery in 8 hours. In humans, the potency of the first homolog, trimethoxyamphetamine, was twice that of mescaline. The next homolog, α -ethylmescaline, at oral levels over 2.5 mg/kg (as the free base) produced neither central activity nor psychic disturbance; its psychotomimetic potency was less than

half that of the first homolog, which suggests that three carbons represent the optimum chain length.

The Dow Chemical Company
Walnut Creek, California

2652 Lindfors, Raimo. Forensic chemical identification of meprobamate by thin-layer chromatography in the presence of sedatives other than barbiturates. Annales Medicinæ Experimentalis et Biologiae Fenniae, 41:355-359, 1963.

This article begins with a brief review of paper and thin-layer chromatographic methods for the identification of meprobamate. Then, a method for the acetone extraction and preliminary water purification of meprobamate and other sedatives from autopsy material is presented. A thin-layer chromatographic method for the purification, separation, and identification of meprobamate in the presence of other sedatives is detailed. In doubtful cases, a double solvent system is recommended. This method has been used in the chemical investigation of 86 cases of suicide by poisoning. A preliminary attempt to identify the metabolic hydroxyl derivative of meprobamate is described.

University of Helsinki
Helsinki, Finland

2653 Marigo, M. Kemijsko-toksikološka istraživanja psihotropnih lijekova. (Chemico-toxicological studies on psychotropic drugs.) Arhiv za Higijenu Rada i Toksikologiju, 13:329-333, 1963.

The uncontrolled and expanding use of psychotropic drugs has produced a high number of poisoning incidents and deaths. A chemical and a pharmacological classification of the psychotropic drugs is given. The drugs are classified into two main groups of psycholeptics and psychoanaleptics. A review is given of the chromatographic methods for the identification of psychotropic drugs. The drugs that have produced the most satisfactory results are recommended as the treatments of choice.

Institute of Medicine
Padova, University
Padova, Czechoslovakia

See also: 2419, 2420, 2428, 2492, 2546, 2552, 2577, 2601, 2604, 2611, 2623, 2632

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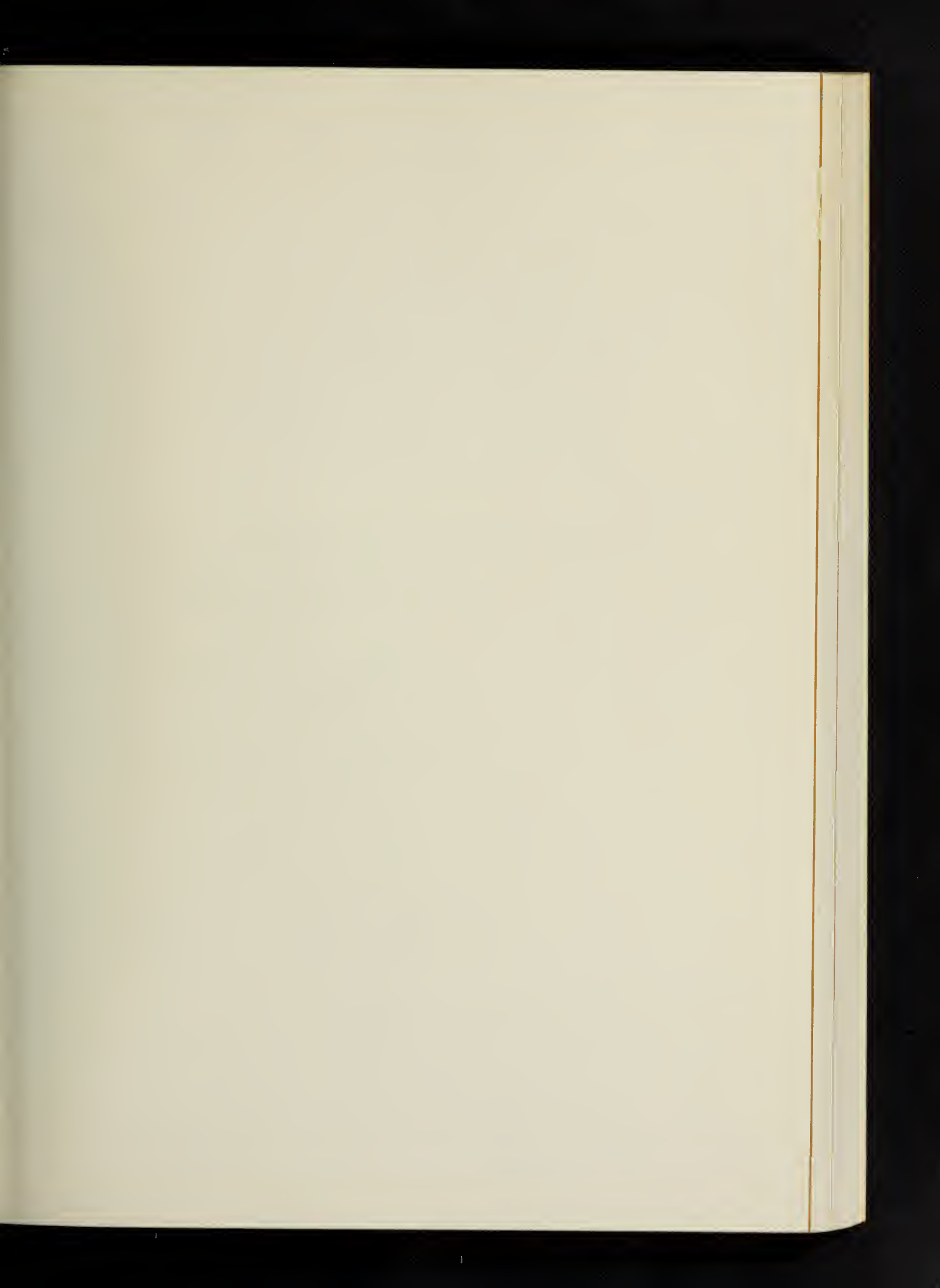
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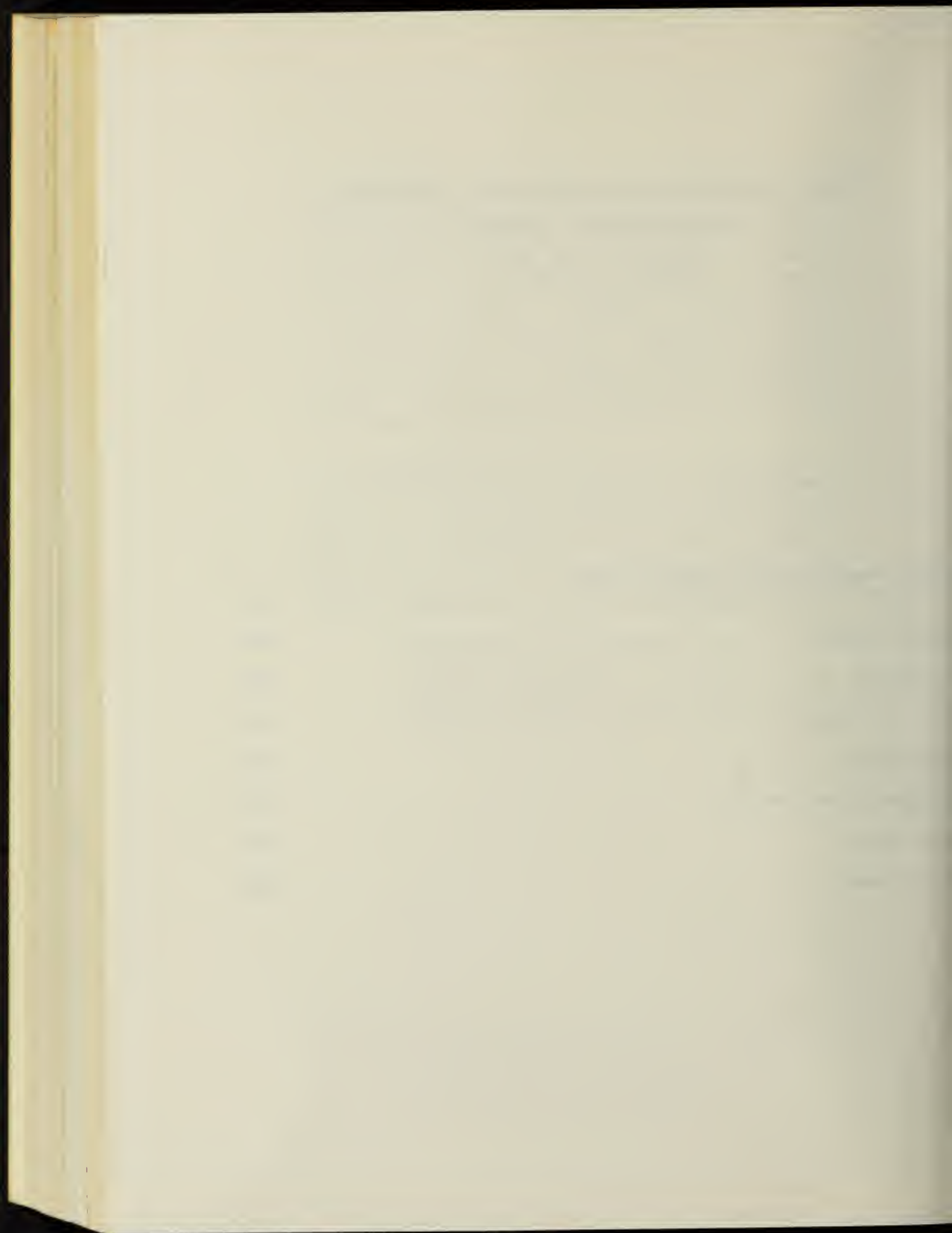
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REVIEWS, SUMMARIES, BIBLIOGRAPHIES, GENERAL ARTICLES AND BOOKS

2654 Smythies, J. R. **Schizophrenia. Chemistry, metabolism and treatment.** Springfield, Illinois, Charles C. Thomas, 1963. 86 p.

The concept of the etiology of schizophrenia, as well as the overall concept of a biochemical etiology, is described. The relation of adrenaline, serotonin, melatonin, and excess methylation hypotheses, which concern the idea that the biochemical lesion is responsible for the illness, are discussed in detail. Results of empirical investigations in the fields of intermediate carbohydrate metabolism, tryptophan metabolism, toxicity of schizophrenic body fluids, and immunological reactions are presented. The psychotomimetic drugs, their mode of action, and their relevance to the problem of the etiology of clinical schizophrenia, are discussed.

Department of Psychological Medicine
University of Edinburgh
Edinburgh, Scotland

2655 Smythies, J. R. **Schizophrenia. Chemistry, metabolism and treatment, Section 2.** Springfield, Illinois, Charles C. Thomas, 1963, p. 12-38.

Free biochemical theories of etiology, based on the chemical relation between mescaline and adrenaline, the antiserotonergic effects of LSD, or the chemical relation between melatonin and harmine, are discussed, and results of research into the biochemical basis of schizophrenia are described. Also, the positive findings in the field of disordered carbohydrate metabolism in schizophrenia are reported. The toxicity of body fluids of schizophrenic rats and mice is reported, and some recent reports of disordered metabolism of various compounds (neuraminic acid, histamine, tryptophan) or classes of compounds (amino acids, indoles) are included in the discussion.

University of Edinburgh
Edinburgh, Scotland

2656 Smythies, J. R. **Schizophrenia. Chemistry, metabolism and treatment, Section 3.** Springfield, Illinois, Charles C. Thomas, 1963, p. 39-55.

Experiments performed using hallucinogenic drugs (LSD, mescaline, brom-LSD, bufotenin, dimethyltryptamine, diethyltryptamine, and psilocybin) are described, and the results are discussed in terms of their importance in the problem of the etiology of schizophrenia and other psychoses.

University of Edinburgh
Edinburgh, Scotland

2657 Root, Walter S. & Hofmann, Frederick G., eds. **Physiological pharmacology. A comprehensive treatise. Volume I. The nervous system—Part A. Central nervous system drugs.** New York, Academic Press, 1963, 703 p.

The effects and mechanisms of action of depressant drugs upon the central nervous system are presented in the Volume I of a series of 10 volumes. The depressant drugs are classified under the following headings: general anesthetics—absorption, distribution, and elimination; the alcohols; sedatives and hypnotics—absorption, fate, and excretion; analgesic and antipyretic drugs—strong and nonnarcotic analgesics; and tranquilizers—phenothiazine, Rauwolfia, and diphenylmethane derivatives. The aspects of tolerance and of physical dependence upon these drugs are also discussed.

Academic Press Incorporated
111 Fifth Avenue
New York, New York

2658 Martin, William R. D. **Analgesic and antipyretic drugs. 1. Strong analgesics.** In: Root, Walter S. & Hofmann, Frederick G., eds. **Physiological pharmacology. A comprehensive treatise. Volume I. The nervous system—Part A. Central nervous system drugs.** New York, Academic Press, 1963, p. 275-305.

Literature concerning the current concepts of pain and the concepts of the modes of action of strong analgesics (morphine-like

agents) is reviewed. The relationship between the chemical structure and the analgesic activity, and absorption, enzymatic alteration, and excretion of the strong analgesics are also discussed.

Addiction Research Center
United States Public Health Service Hospital
Lexington, Kentucky

- 2659 Seevers, Maurice H. & Deneau, Gerald A. **F. Physiological aspects of tolerance and physical dependence.** In: Root, Walter S. & Hofmann, Frederick G., eds. *Physiological pharmacology. A comprehensive treatise. Volume I. The nervous system—Part A. Central nervous system drugs.* New York, Academic Press, 1963, p. 565-640.

Types of tolerance to and physical dependence on morphine and alcohol are discussed. Tolerance and dependence are also described in relation to other depressants, such as phenacetin and dextrorphan tartrate. A distinction in meaning is made between tolerance and physical dependence. (195 references)

Department of Pharmacology
University of Michigan
Ann Arbor, Michigan

- 2660 Bradley, P. B. E. **Tranquilizers. 1. Phenothiazine derivatives.** In: Root, Walter S. & Hofmann, Frederick G., eds. *Physiological pharmacology. A comprehensive treatise. Volume I. The nervous system—Part A. Central nervous system drugs.* New York, Academic Press, 1963, p. 417-472.

The chemical structure of phenothiazine derivatives is discussed, and examples of derivatives with central actions are given. Chlorpromazine is used as a model for describing the physiological, biochemical, and psychological actions of this series of compounds. The combination of chlorpromazine with other drugs and the site and mode of action of the drug in the CNS are discussed. Other phenothiazines with mainly central actions are described. The effects of phenothiazines in man are summarized.

Department of Experimental
Neuropharmacology
University of Birmingham
Birmingham, England

- 2661 Stolman, Abraham, ed. **Progress in chemical toxicology. Volume 1.** New York, Academic Press, 1963. 436 p.

New analytical techniques in the field of chemical toxicology are described, and the underlying methodology and toxicological significance are discussed. The following 11 general areas are presented: (1) isolation and separation techniques for identification of poisons; (2) application of gas chromatography to toxicology; (3) aliphatic alcohols; (4) acidic and neutral poisons; (5) ataraxics and nonbarbiturate sedatives; (6) determination of antiarthritics, antihistamines, and thymoleptics; (7) narcotics and related bases; (8) toxicity of air pollutants; (9) analytical methods for air pollutants; (10) poisonous mushrooms; and (11) poisonous seeds and fruits.

Academic Press Incorporated
111 Fifth Avenue
New York, New York

- 2662 Farmilo, Charles G. & Genest, Klaus. **Narcotics and related bases.** In: Stolman, Abraham, ed. *Progress in chemical toxicology. Volume 1.* New York, Academic Press, 1963, p. 199-285.

Recently developed methods for the quantitative and qualitative determination of narcotics as reported in the literature are described. Brief reference is made to methods of isolation from tissues and identification of metabolites and unchanged narcotics in studies on metabolism. The following areas are discussed in detail: (1) physicochemical methods for the identification of narcotics and related bases; (2) assay, characteristics, composition and origin of opium; and (3) identification and origin of cannabis (marihuana). (315 references)

Food and Drug Directorate
Department of National Health and Welfare
Ottawa, Canada

- 2663 Spiegel, E. A., ed. **Progress in neurology and psychiatry.** An annual review. Volume XVII. New York, Grune & Stratton, 1962, 607 p.

Nearly 5,000 publications concerning research in psychiatry, the basic sciences of neurology, and neurosurgery have been surveyed in the form of an annual review. This volume also contains several biennially

viewed subjects, such as neurophysiology (electrophysiological aspects), the vascular system, and shock treatments.

Temple University
School of Medicine
Philadelphia, Pennsylvania

64 Kapp, Frederic T. & Gottschalk, Louis A. **Drug therapy.** In: Siegel, E. A., ed. *Progress in neurology and psychiatry. An annual review. Volume II.* New York, Grune & Stratton, 1962, 536-558.

The psychopharmacologic agents were divided into four categories (major tranquilizers, minor tranquilizers, antidepressants, and psychomotor stimulants) and were discussed in terms of their uses, properties, effects, toxicity, and side effects. The recommended daily dosages and other pertinent data drawn from clinical studies were also included. (290 references)

Temple University
School of Medicine
Philadelphia, Pennsylvania

65 Cerletti, A. **Synopsis of certain developments within the field of hallucinogenic drugs.** In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. *Hallucinogenic drugs and their psychotherapeutic use.* Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. First session, 1-3.

Brief history of certain hallucinogenic drugs---mescaline, LSD, psilocybin, and mescaline acid amide---is given. It has been found that all of these drugs are chemically related to LSD. Since the basic chemical structure of LSD, which is not of natural origin, has been found in one of the most natural hallucinogenic drugs (mescaline), it may be concluded that the different hallucinogens are indeed related chemically, as well as in other aspects.

Pharmaceutical Laboratories
Sandoz Products A.G.
Basel, Switzerland

2666 McKellar, Peter. **Mescaline and human thinking.** In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. *Hallucinogenic drugs and their psychotherapeutic use.* Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. First session, p. 12-16.

Several mescaline experiments are described, and the observations made are given. The way in which mescaline experiments may be used in studying the phenomena of human thinking is illustrated. The following phenomena are discussed: psychotic, mystical, and normal thinking; deterioration of intellectual standards; associative thinking, concretization; delusions; and problems of communication.

Department of Psychology
University of Sheffield
Sheffield, England

2667 Sandison, R. A. **Certainty and uncertainty in the LSD treatment of psychoneurosis.** In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. *Hallucinogenic drugs and their psychotherapeutic use.* Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. Second session, p. 33-36.

Several principles are formulated about the psychotherapeutic relationship between the patient and the therapists during LSD therapy. Uncertainties concerning LSD treatment of psychoneurosis are classified and examined.

Pockwick Hospital
Worcester, England

2668 Lambert, Carl. **Technique in the use of phencyclidine.** In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. *Hallucinogenic drugs and their psychotherapeutic use.* Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. Third session, p. 79-93.

Phencyclidine was used in the treatment of 10 neurotic outpatients, six women and four men, 30 to 55 years of age. The patient

sample included subjects with specific obsessional rituals, obsessional personalities, anxiety states with depressive mood swings, and phobias. At the first session, the patients were given 2.5 mg phencyclidine over a 5- to 10-minute period. Dosage was increased every two sessions, until a maximum of 5 mg phencyclidine was given. Patient response is categorized into four phases: (1) acute phase; (2) communicative phase; (3) euphoric—relaxed phase; and (4) depressed—irritable phase. Each phase is described in detail. The average duration of phencyclidine treatment was about 3 months, and the average number of injections was eight. Eight patients responded favorably, but two showed no lasting benefit.

London, England

- 2669 Eisner, Betty Grover. **The influence of LSD on unconscious activity.** In: Crockett, Richard, Sandison, R. A., & Walk, Alexander, eds. *Hallucinogenic drugs and their psychotherapeutic use.* Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. Fifth session, p. 141-157.

A technique for using LSD therapy in the treatment of mental illness is described. The number of LSD sessions varies according to the individual and his condition. Sessions occur at weekly intervals, starting with a minimal dosage of 25 µg, and increasing by increments of 25 µg until optimum dosage, usually 100 µg to 150 µg, is reached. The addition of 10 to 40 mg Ritalin i.m. or i.v. is used to enhance and sustain the LSD reaction in certain cases. The LSD reaction is stopped by giving, concurrently, 1.5 grains seconal and 50 mg chlorpromazine. The setting for the session is described. Techniques that enhance the revelation of the patient's subconscious under LSD are discussed. The importance of nonverbal communication is stressed.

Los Angeles, California

- 2670 De Groot, M. H. **The role of hallucinogens in depersonalization and allied syndromes.** In: Crockett, Richard, Sandison, R. A., & Walk, Alexander, eds. *Hallucinogenic drugs and their psychotherapeutic use.* Proceedings of the

Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. Fourth session, p. 97-100.

The use of hallucinogens in the treatment of the depersonalization syndrome is reported based on case histories presented in the literature. The syndrome is defined according to Ackner (1954). A report is given of the successful use of *Cannabis indica* in the treatment of a female patient with depersonalization, derealization, and disordered time perception of 6 months' duration. This patient was unsuccessfully treated with pentothal and methedrine injections and with a single ECT. She was then given 4 grains of *Cannabis indica*; at the second session, she was given 3 grains of the drug. Following this treatment, the patient, was completely improved and, to date, has not relapsed. Various other cases treated with mescaline, *Cannabis indica*, and LSD, either alone or in combination, are reviewed. None showed the dramatic improvement noted in the previous case. Cases with a long history of depersonalization have a poor prognosis. Hallucinogenic drugs appear to have little therapeutic value in these personality disorders, except as adjuncts to intensive psychotherapy.

York Clinic
London, England

- 2671 Crockett, Richard, Sandison, R. A., & Walk, Alexander, eds. *Hallucinogenic drugs and their psychotherapeutic use.* Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. 191 p.

The proceedings are reported of the quarterly meeting of the Royal Medico-Psychological Association, at which papers concerned with the general topic of hallucinogenic drugs were given. The first session of the conference was devoted to the relationship of hallucinogens to other, both naturally occurring and synthetic, chemical substances. The clinical applications of the hallucinogenic drugs were the main topics of the second session, and the actual techniques and methodology were outlined and discussed during the third session. The use of hallucinogens in specific conditions was the topic of the fourth session, with special attention being given to LSD. The fifth session was devoted to actual clinical

observations and phenomenological interpretations. In the final session, an attempt was made to examine the wider implications of the hallucinogenic drugs for mankind, in relation to philosophical, ethical, and religious issues.

Charles C. Thomas
Springfield, Illinois

672 Taylor, Gordon Rattray, Mortimer, Raymond, Mayhew, Christopher, & Huxley, Francis. The moral, religious and social significance of experience under hallucinogenic drugs. In: Crockett, Richard, Sandison, R. A., & Walk, Alexander, eds. Hallucinogenic drugs and their psychotherapeutic use. Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. Sixth session, discussion, 161-186.

Speeches by four men, concerning their experiences under hallucinogenic drugs, are presented. Three men took mescaline, and one had taken both LSD and mescaline. A discussion of these reports by members of the audience is given. The wide variation in the responses to these drugs is stressed.

the Cassel Hospital
London, England

73 Waelsch, H. Protein metabolism of the nervous system. Schweizer Medizinische Wochenschrift, 93(37):1289, 1963.

The protein metabolism of the nervous system was discussed, and experiments were described that concerned a heterogeneous mixture of proteins derived from many structural units of the whole brain or of certain brain areas and that concerned the metabolism of families of particular proteins. The protein metabolism of the nervous system resembles, in many aspects, the protein metabolism of any mammalian organ, whereas in others it has specific features applicable only to the nervous system. Further studies of protein metabolism in the nervous system will be of great significance for the understanding of the function of this organ in health and disease.

Columbia University
New York, New York

2674 Marrazzi, Amedeo S. The generality of cerebral synaptic drug response and its relation to psychosis. Recent Advances in Biological Psychiatry, 6:1-8, 1963.

Methods of studying the responses of synapses, which are sites most vulnerable to chemicals and drugs, are described. The synaptic homeostasis operates in the cortical, subcortical, and brainstem reticular regions and the synaptic humorally determined homeostasis can be distorted by psychotogens. It is inferred that cerebral synapses, in general, react to drugs and chemicals in a qualitatively identical manner, with great quantitative differences. Excitation and inhibition at the cellular level are discussed. The disposition of cerebral synaptic thresholds in particular neuronal networks determines behavior. The hypothesis is made that the distortion of homeostasis in the neurohumoral environment of the synapses is of central importance. The generality of synaptic responsiveness to drugs accounts for their extensive cerebral actions, while the differences in synaptic thresholds are responsible for the particular form of the failure of cerebral homeostasis induced by chemicals and drugs.

(No address)

2675 Grof, Stanislav, Vojtechovsky, Milos, Vitek, Vladimir, & Prankova, Slavka. Clinical and experimental study of central effects of adrenochrome. Journal of Neuropsychiatry, 5(1):33-50, 1963.

The central effects of *L*-adrenochrome and *d,L*-adrenochrome were observed in 18 Wistar rats (200 g in weight) and in 15 human subjects, 6 females and 9 males, 17 to 38 years of age, 5 of whom were neurotics or psychopaths and 10 of whom were normal. The rats were given *L*-adrenochrome in doses of 6 to 8 mg/kg. The drug inhibited spontaneous motor activity and prolonged the latency periods of conditioned reflexes. Both adrenochrome preparations were given in doses of 15 or 30 mg p.o. Nine patients received both preparations. The control substance was *S*-azorubine. The patients' responses were assessed by the following: psychiatric interview, blood pressure, pulse rate, FF test, time estimation, an association test, the Clyde Mood Scale, and Stroop's questionnaire. In high doses, adrenochrome caused transient psychotic reactions; in lower doses, neurotic reactions were frequent. Six subjects were given an additional 20-mg dose of adrenochrome p.o.,

and the EEG's were recorded. In five subjects, EEG changes were noted, but the changes did not correlate with the intensity of psychotic changes.

Psychiatric Research Institute
Prague, Czechoslovakia

- 2676 Perkow, W. **Konstitution und Wirkung biologisch aktiver Verbindungen.** (16. Mitteilung. Eine arbeitshypothese.) (Constitution and action of biologically active compounds. Report number 16. A hypothesis.) *Pharmaceutica Acta Helvetiae*, 38(7-8):385-406, 1963.

Compounds with biological activity are reviewed to determine possible common structural elements that may form the basis of the biological activity. The compounds reviewed were found to possess a "biologically active center," characterized by a greatly reduced electron density. This biologically active center serves as the site of metabolic action with physiological receptors when in a spatially suitable configuration. The function of this center is explained as an exchange system between molecular parts equivalent in regard to energy and biochemistry. Groups attached to this center determine solubility properties, site of resorption, and specific action. Eighty-one compounds and many molecular components are discussed as examples of this theory.

Hamburg, Germany

- 2677 Kusch, T. & Heinrich, I. **Die Aktivitätsveränderungen der Leber-Tryptophan-Pyrrolase und Tyrosin- α -Ketoglutarat-Transaminase durch Chlorpromazin und Reserpin unter Berücksichtigung der Funktionen der Nebennieren.** (Modification of the activity of liver tryptophan-pyrrolase and tyrosine- α -ketoglutarate transaminase by chlorpromazine and reserpine with reference to adrenal gland function.) *Acta Biologica et Medica Germanica*, 10:554-560, 1963.

The effect of chlorpromazine and reserpine on the activity of the liver enzymes tryptophan pyrrolase (TP) and tyrosine- α -ketoglutarate-transaminase (TKT) was determined in intact and in adrenalectomized Wistar rats. In intact rats, chlorpromazine, in massive and in therapeutic doses, produced a considerable increase in TP activity. Adrenalectomy completely suppressed the chlorpromazine effect. In intact rats, both

chlorpromazine and reserpine caused a pronounced increase in TKT activity, even in low dosages. In adrenalectomized rats, the chlorpromazine effect was weakened, but the reserpine effect was not inhibited.

Institute for Pharmacology
Friedrich-Schiller University
Jena, Germany

- 2678 Kielholz, P., Labhardt, F., Battegay, R., Rümmele, W., & Feer, **Therapie der Depressionen und der depressiven Krankheitszustände.** (Treatment of depressions and depressive states.) *Deutsche Medizinische Wochenschrift*, 88(16):1617-1623, 1963.

In the treatment of depressive states, antidepressive pharmacotherapy, in addition to the usual psychotherapy and somatic therapy, is useful. Monoamine oxidase inhibitors and phenothiazines are excellent antidepressives. Drugs with limited antidepressive effects include neuroleptics, tranquilizers, stimulants, and hormones. The side effects of these drugs are discussed. An indication is made as to the drugs of choice in the treatment of lethargy, fear, agitation, insomnia, and vegetative symptoms. The dosages, combinations of therapies, length of therapy, and the problems of prolonged treatment are discussed. Important basic principles in the treatment of several depressive states are given.

Psychiatric University Clinic
Basel, Switzerland

- 2679 Hoff, Ebbe Curtis. **Current advances in the ambulatory medical treatment of alcoholics.** *Academy of Medicine of New Jersey Bulletin*, 9(3):143-153, 1963.

In the ambulatory care of alcoholics, a conservative policy of drug use is indicated to avoid the transfer of addiction from alcohol to sedatives, tranquilizers, or addictive modalities. Many pharmacological adjuncts in the comprehensive therapy of alcoholics have been used effectively, however. Disulfiram may be taken to reinforce the patient's motivation for a day-to-day program of sobriety. Metabolic support in the treatment of alcoholics includes massive polyvitamin supplementation and hormones. Chlordiazepoxide (10 mg t.i.d. to 25 mg q.i.d.) and diazepam (10 mg 4 or 5 times daily) are valuable in the care of the acutely

intoxicated patient, in preventing withdrawal symptoms, such as delirium tremens, and in shortening postalcoholic distress. Psycho-
 delic drugs (LSD) and aversion therapy, when administered by a well-trained staff, may be used in the treatment of alcoholics.

Virginia State Health Department
 Richmond, Virginia

2680 Agin, Henry V. **Tranlycypromine in depression: A clinical report.**
 American Journal of Psychiatry, 117:150-151, 1960.

A clinical study was conducted to test the efficacy of tranlycypromine in the treatment of 44 depressed patients, 34 men and 10 women, 20 to 71 years of age, mean age, 46. The diagnoses of the patients were reactive depression, involutional depression, manic depression, cyclothymic depression, and obsessive compulsive with depression. The patients studied had not responded to previous drug treatment or psychotherapy. Alkaline phosphatase, cephalin flocculation, and/or serum glutamic oxalacetic transaminase tests were made before and during drug treatment. Most of the patients received initial doses of tranlycypromine (10 to 50 mg/day), in divided doses of 30 to 60 mg. After 5 to 7 days of treatment, the dosage was reduced by 10 mg. There was further reduction of dosage (10 mg) at weekly intervals, until a dosage of 30 mg/day or less was administered. All the patients underwent nonanalytic psychotherapy throughout the treatment period (2 to 3 months). In addition to tranlycypromine, tranquilizers were given to six patients and T was given to four. Treatment results were as follows: satisfactory results in 10 patients and unsatisfactory results in 34 patients. Optimal results were achieved in 14 days after treatment began. In 17 patients, the following side effects were noted: headache, insomnia, dizziness, constipation, drowsiness, leg cramps, nausea, and anorexia. These effects occurred at doses over 40 mg/day. It was concluded that in 10 patients who failed to respond to therapy had symptoms of anxiety, which limited the beneficial effect of tranlycypromine.

Eastern Parkway
 Brooklyn, New York

2681 Vincent, P., Giroud, M., & Chevallier, A. **L'assistance respiratoire dans les comas toxiques.** (Respiratory assistance in toxic coma.) Journal de Médecine de Lyon, 44:407-420, 1963.

The treatment of toxic-coma patients by maintenance of correct oxygenation is discussed, based on 30 poisoning cases, 15 sedative poisonings, and 15 acute carbon-monoxide poisonings. In CO poisoning cases, the patient is given oxygen under pressure, with assisted respiration if necessary, and glucose perfusion. Respiratory assistance may have to be continued for several weeks, depending on the degree of damage caused by anoxia. In sedative poisonings, two factors are necessary for successful treatment—maintenance of adequate ventilation and elimination of the toxic agent. Respiratory assistance in such cases is described. The following three techniques for eliminating the toxic agent are discussed: (1) extrarenal blood purification; (2) forced diuresis; and (3) alkalinization. (38 references)

(No address)

2682 Govaerts, Jane. **Quelques incidents thérapeutiques récemment signalés en neuropsychiatrie.** (Several therapeutic accidents recently reported in the field of neuropsychiatry.) Medecin Libre, 35:48-50, 1961.

Several therapeutic difficulties encountered with the use of neuropsychiatric drugs are discussed. Diphenylhydantoin can produce neurological effects, hypertrophic gingivitis, and a syndrome simulating lymphosarcoma. Trimethadione occasionally causes alopecia. Neuroleptics, in general, cause hepatic syndrome, skin symptoms, orthostatic hypotension, constipation, polyneuritic symptoms, suicidal tendencies, sexual inhibition or the correction of impotence, and varied extrapyramidal syndromes. These effects are thought to be favorable to therapy in certain cases, are not dose dependent, and are reversible upon stopping treatment. In many cases, therapy may be continued after administration of certain corrective drugs. Promethazine HCl (25 mg i.m.), for example, rapidly corrects acute hypertonic phenomena. Parkinsonian manifestations may be controlled by isothiazine, and Parkinsonian syndromes may be prevented by alimenazine (150 to 450 mg/day). Other drugs that

control psychic or somatic side effects include methylphenidate, centrophenoxine, heptamyl, prostigmine, and pyridostigmine. Also, difficulties caused by excessively large doses of certain analgesics, piperazines in children, and vitamin A are described.

Medical Inspector of the Schools
Paris, France

2683 Doumic, Jacques-Max. *Survol des anorexigènes.* (Survey of the appetite depressants.) *Vie Médicale*, 44:69-87, 1963.

The three general groups of appetite depressants (amphetamines, morpholine derivatives, and amphetamine derivatives) are discussed in terms of their use, chemical composition, properties, and general effects. In order to define their particular uses more clearly, a distinction was made between hunger, appetite, and satiety. The appetite depressants have a definite effect on the hypothalamus, but the mechanism of a related depressant effect on the lateral centers that stimulate the appetite is not clear. Some criticisms of the use of the drugs are discussed in conjunction with the possibilities of toxicity and of a lack of tolerance to the drugs.

(No address)

2684 Frommel, E., Seydoux, J., & von Ledebur, I. *Quel est l'antidote de l'excitation psychomotrice de l'éthylique? Phénobarbital, morphine, Librium ou chlorpromazine? Etude expérimentale.* (What is the antidote for the psychomotor excitation of the alcoholic? Phenobarbital, morphine, Librium or chlorpromazine? Experimental study.) *Comptes Rendus des Séances de la Société de Biologie et de Ses Filiales*, 157:526-529, 1963.

The effects of phenobarbital, morphine, chlordiazepoxide, and chlorpromazine on the duration of ethanol-induced sleep were tested in guinea pigs. The animals were given 5 cc/kg of a 60% ethyl alcohol solution, and the blood-alcohol curves were determined. The animals were then given one of the test drugs, in the following doses, simultaneously with alcohol: 30 mg/kg phenobarbital p.o.; 13.5 mg/kg morphine s.c.; 10 mg/kg chlordiazepoxide p.o.; or 30 mg/kg chlorpromazine s.c. The

duration of sleep caused by alcohol was increased significantly by morphine and by phenobarbital. Chlordiazepoxide had no significant effect on alcohol-induced sleep. Chlorpromazine did not significantly alter the duration of sleep in guinea pigs weighing less than 800 g, but it significantly shortened sleep in animals weighing more than 800 g. Chlordiazepoxide and chlorpromazine are superior to the classic antidotes, morphine and phenobarbital, in the treatment of alcohol-induced psychomotor agitation, since they do not show the potentiation of sleep exhibited by morphine and phenobarbital.

Institute of Experimental Therapy
Medical School
Geneva, Switzerland

2685 Lespagnol, Albert & Lespagnol, Charles. *Acquisitions thérapeutiques récentes dues à la synthèse chimique.* (Recent therapeutic acquisitions due to chemical synthesis.) *Produits et Problèmes Pharmaceutiques*, 18(6):279-294, 1963.

The recently synthesized pharmaceutical compounds are listed and described briefly; their structural formulas and properties are included. The hypnotics, hypnosedatives and tranquilizers discussed include alcoholurethanes, amides, ureides, imides, barbiturates, hydantoines, oxazolindines, and piperidine derivatives. The antihistaminic neuroplegics discussed include phenothiazine derivatives, piperazine, and benzyldrol derivatives. Antibacterial, hypoglycemic, and diuretic sulfamides are also included.

School of Medicine and Pharmacy
Lille, France

2686 Bremer, Frédéric. *Considérations sur les processus d'inhibition centrale.* (Thoughts on the process of central inhibition.) *Archives Internationales de Pharmacodynamie et de Thérapie*, 139(1-2):152-158, 1962.

The author reviews the literature on and discusses the development of the terms "presynaptic" (central indirect) and "postsynaptic" (central direct) inhibition at the spinal level. This distinction at present is considered definitive. The problems briefly discussed in this connection include immediate determination

f inhibitory processes, their pharmacological properties, functional significance, and participation in inhibitory processes originating in supraspinal agglomerations of neurons, particularly in the cerebral cortex.

laboratory of General Pathology
University of Brussels
Brussels, Belgium

2687 Freund, K. The concept of psychopathology. *Ceskoslovenska Psychiatrie*, 9(4):246-247, 1963.

A discussion is presented of the vast discrepancies that exist in the use of the term "psychopathia." A suggestion is made to abandon this term, as it no longer means anything and is often confused with neurosis and with psychotic diseases.

(No address)

2688 University of São Paulo. Role of various brain structures on physiological functions. Final report, São Paulo, Brazil, 12 June, 1964, 27 p. Contract AF-AFOSR-311-63, unclassified report.

This report includes 15 studies, as follows:

- (1) Effects of lesions of amygdala and subcommissural organ on sodium chloride and water intake in the rat; (2) Effects of adrenalectomy on rats with a low ingestion of sodium chloride due to hypothalamic lesions; (3) Septal regulation of blood pressure in the cat: effects of different parameters of stimulation and of occlusion of carotid arteries; (4) Pharmacological studies on the depressor blood arterial effect after septal stimulation in the cat; (5) Effects of stimulation of septal area on blood pressure and respiration in the rat; (6) Baroreceptor activity in chronic renal hypertensive rats; (7) Carotid occlusion in the rat: circulatory and respiratory effects; (8) Neurogenic hypertension in the rat; (9) Electrophysiological investigation of the chronic auditory toxicity of kanamycin and aminosidine; (10) Sexual-motor integration in the chloralosed rat; (11) Influence of sexual hormones on the excitability of cerebral cortex; (12) Effects of hemidecortication on placental delivery in the rat; (13) The effects of sexual hormones on the avoidance

responses; (14) The action of bradykinin on the avoidance response; and (15) Lipogenesis "in vivo" after total pancreatectomy of the rat.

Faculty of Medicine of Ribeirão Preto
The University of São Paulo
São Paulo, Brazil

2689 Lyskanowski, Marcin. *Kartki z dziejów psychiatrii. Z zagadnień farmakologicznego leczenia psychiatrycznego w Polsce w XIX stuleciu.* (Pages from the history of psychiatry. On problems of pharmacological psychiatric therapeutics in Poland during the 19th century.) *Neurologia, Neurochirurgia i Psychiatria Polska*, 13(1):107-109, 1963.

A brief review of pharmacological therapy that was popular among Polish physicians in the 19th century is given. The two most widely used therapies were emetics and digitalis combined with other drugs in simple syrup. Bloodletting and cold baths were common and frequent treatments, although some physicians disputed their efficacy. Some of the more barbaric treatments used in France, England, and Germany at that time were condemned among Polish physicians. Other therapies mentioned included sweet mercury, opium, camphor, belladonna, curare, calabrus, erythroxulon coca, and, toward the end of the century, electrotherapy.

State Hospital for Nervous and
Psychic Diseases
Drewnica, Poland

2690 Moldenhauer, Berthold. *Butyrylperazin in der Neuropsychiatrie.* (Butyrylperazine in neuropsychiatry.) *Medizinische Welt*, 3(22):1-12, 1961.

Butyrylperazine (Randolectil) was tested on 125 psychiatric patients. Diagnoses in the patient sample included 92 with schizophrenia, 10 with manic depression, 4 with paranoid-hallucinatory syndrome subsequent to brain damage, and 19 with senile paranoid depression. The drug generally was given parenterally for the first 3 days of treatment, and then was administered orally. Dosage was usually 30 mg daily, but in some cases, up to 60 mg was given daily. Average duration of treatment was 12 weeks. The drug was

particularly effective in acute cases of schizophrenia, in schizophrenics who had experienced two or more relapses, and in manic-depressive disorders. The drug was ineffective in depressives suffering from cerebral arteriosclerosis. Side effects included insomnia, reduction in basic drive, and a tendency to emotional indifference. Extrapyramidal effects were frequent, appearing a few hours after the first injection. These effects were easily controlled with beiperiden.

Karl-Bonhoeffer City Hospital
Berlin-Wittenau, Germany

- 2691 Bryk, Barbara & Moldenhauer, Berthold. **Kombinationstherapie schwerer manischer und manieformer Erregungszustände mit Megaphen-Randolectil.** (Treatment of acute manic and manic-type excitation states with the chlorpromazine-butyrylperazine combination.) *Medizinische Welt*, 25:1426-1427, 1962.

Therapeutic evaluation of the use of a combination of butyrylperazine and chlorpromazine in the treatment of 15 patients with manic or manic-like excitation was made, including patients who were alcoholics, residual schizophrenics, or paranoiacs. The drug produced a calming effect within a half hour, and a definite hypnotic effect was observed after the treatment of the most pronounced manic excitation. No side effects were observed.

Karl Bonhoeffer City Hospital
Berlin-Wittenau, Germany

- 2692 Persic, Nikola. **Psychiatry in the Soviet Union.** *Lijeckicki Vjesnik*, 85(7):747-758, 1963.

This article includes a discussion of the following topics: The History of Psychiatry in the Soviet Union, Basis for Scientific and Investigative Work in Psychiatry, State and Principles of Organization of Psychiatric Care, and Medical Training and Post Graduate Training.

(No address)

- 2693 Galdiero, F. **Azione della clorpromazina sulla crescita del *Bacillus subtilis*.** (Action of chlorpromazine on the growth of *Bacillus subtilis*.) *Rivista dell'Istituto Sieroterapico Italiano*, 38:80-88, 1963.

The effect of various concentrations of chlorpromazine on the growth of *Bacillus subtilis* in a liquid agar medium was tested. In the medium without chlorpromazine, *B. subtilis* grew vigorously and formed spores within 72 hours. With 250 µg/ml chlorpromazine, growth was completely inhibited. With 50 µg/ml, filamentous growth occurred within 72 hours, gigantic cell forms appeared, but no spore formation was noted. At 10 µg/ml to 50 µg/ml, extremely filamentous growth without spore formation was observed; no large cells were seen. When 500 µg/ml Mn^{++} was added to the chlorpromazine medium, the growth-limiting effect of chlorpromazine was partially inhibited. When 50 µg/ml Mn^{++} was added to the medium that did not contain chlorpromazine, the bacteria formed spores within 72 hours. The effects of chlorpromazine are attributed to an influence on cell-wall synthesis.

University of Naples
Naples, Italy

- 2694 Hanau, Rino. **Contributo clinico alla conoscenza della sindrome extrapiramidale da neuroplegici.** (Clinical contribution to the knowledge of the extrapyramidal syndrome caused by neuroplegics.) *Rivista di Patologia Nervosa e Mentale*, 84:76-88, 1963.

Factors that might predispose an individual to extrapyramidal reactions during the course of neuroleptic therapy were examined. A comparison was made between 41 chlorpromazine-treated patients who exhibited extrapyramidal reactions (33 parkinsonian, 6 dyskinetic, and 2 akathisia) and 180 chlorpromazine-treated patients who showed no extrapyramidal reactions. The patients were receiving from 100 to 300 mg chlorpromazine daily, and they had been treated for at least 30 days. No causal relationships were found relating to sex, age, psychopathic or parkinsonian heredity, psychopathological state, or associated therapeutic measures. A frequent association was noted between the presence of a pre-existing cerebral lesion and the development of extrapyramidal symptoms.

Clinic of Nervous and Mental Diseases
University of Bari
Bari, Italy

695 Hanau, Rino. "Placebo" "azione placebo" ed "effetto placebo." "Placebo," "placebo action" and "placebo effect.") *Sistema Nervoso*, 15:53-70, 1963.

The author reviews the literature on and discusses the concepts of placebo, placebo action, and placebo effect. It appears that every drug is accompanied by a certain suggestive action in addition to its proper biochemical action. Other factors involved in the production of the placebo effect are related to the person receiving treatment, to the administering physician, the therapeutic environment, etc. (51 references)

Clinic of Nervous and Mental Diseases
University of Bari
Bari, Italy

696 Taibi, Gerlando. *Il lisozima in neuropsichiatria. (Rassegna sintetica-clinica).* (The use of lysozyme in neuropsychiatry. (Clinical synthesis and review).) *Lavoro Neuropsichiatrico*, 32(3): 41-474, 1963.

A review is given of the literature on lysozyme, a bacteriolytic enzyme first recognized by Fleming (1922), primarily concerning the effect of this enzyme in the treatment of neuropsychiatric ailments. Chemical composition, pharmacological effects, and three possible mechanisms of action of the enzyme are described. Lysozyme has been used to treat diseases of the peripheral nervous system (*Herpes zoster* infections, facial paralysis, and trigeminal neuralgia). The author's experience in treating 15 patients with *Herpes zoster* (75 to 150 mg lysozyme daily) and 12 patients with facial paralysis (150 mg daily) is discussed. Lysozyme has also been used to treat diseases of the spinal cord, neuritis, diseases of extrapyramidal origin (Sydenham's chorea), encephalopathies, and confusional psychoses. The author's treatment of cases of sclerosis, Sydenham's chorea, and confusional psychosis using lysozyme is reported. (95 references)

Provincial Psychiatric Hospital
Grigento, Italy

697 Yoshiharu, Aoki. (Recent advance in research of drug addiction in Japan.) *Sogo Igaku Medicine*, 20(1):82-5, 1963.

The increasing problem of drug addiction in Japan is presented, based on statistics reported in the literature. The incidence

of addiction to central stimulants, hypnotics, narcotics (both medical and unlawfully imported), antihistamines, and tranquilizers is discussed. Withdrawal symptoms for the various drugs are described. The incidence of addiction to more than one drug is reviewed. Of 160 cases seen from 1950 to 1959, 61% were addicted to two kinds of drug, 24% to three kinds, 11% to four kinds, and 3% to five kinds. Precipitating factors in cases of drug addiction were failure in school or in jobs, economic problems, personality disorders, and poor environment. The treatment of drug addiction is described.

Sobu Mental Hospital
Hunabashi, Japan

2698 Smetankin, G. N. *Third Volga conference of physiologists, biochemists and pharmacologists.* *Zhurnal Vysshey Nervnoy Deyatel'nosti*, 13(6):1108-1110, 1963.

A summary of the reports presented at the Third Volga Conference of physiologists, biochemists, and pharmacologists is given. The reports included various questions concerning physiology, biochemistry, pharmacology, the CNS and higher nervous activity, cardiovascular system, respiration, endocrinal system, digestion, physiology of domestic animals, and the physiology of work and sport.

(No address)

2699 Whitley, E. K. *Barbiturates and synergistic drugs.* *Medico-Legal Bulletin*, 126:1-4, 1963.

Drugs known to enhance the depressant action of barbiturates are discussed. The following drugs are mentioned: acetophenetidin; the anesthetic agents nitrous oxide, ethyl ether, and cyclopropane; morphine, alcohol, calcium salts, acetylcholine, tetraethylthiuran disulfide, mephenesin, thiamine, chlorpromazine, MAO inhibitors, reserpine, and combined meperidine-promethazine. The knowledge that these drugs (tranquilizers, antihistamines, alcohol, antihypertensives, and analgesics), when combined with sublethal doses of barbiturates, can be lethal should be stressed.

Medical College of Virginia
Richmond, Virginia

- 2700 Nakazawa, Tsuneyuk, Tominaga, Jun, & Kabeshima, Akio. (**Therapeutic studies on arteriosclerotic psychosis.**) Brain and Nerve, 15(1):91-95, 1963.

The clinical effect of vitamin B₆ on the psychic disorder that is related to arteriosclerosis was investigated. Results showed improvement in insomnia, depression, anxiety, emotional disorder, forgetfulness, and aphasia. The complex disorders in cerebral arteriosclerotic disease cannot be treated only by vitamin B₆; other medications must also be used in a therapeutic regime. However, B₆ does have an important role in the improvement of brain metabolism.

Department of Neuropsychiatry
Keio University School of Medicine
Tokyo, Japan

- 2701 Ivanova, N. N. & Shteyn, V. V.
O profilaktike aminazinovykh
dermatitov sprovotsirovannykh insolyatsiyey.
(On the prevention of Aminazine dermatitis
induced by solar radiation.) Zhurnal
Nevropatologii i Psikhiatrii imeni S. S.
Korsakova, 63:440-442, 1963.

The problems and treatment of dermatoses induced by a combination of chlorpromazine and solar radiation were investigated in 125 women, 30 to over 60 years of age, with chronic psychic disorders that had lasted from 2 to 15 years. Moderate and severe cases of dermatoses developed after a minimum of 6 months of chlorpromazine therapy. Exposure to extreme sunlight plus chlorpromazine and vitamin therapy caused the development of the following degrees of cutaneous lesions in 84 patients---slight (33), moderate (27), and serious (24). No incidents of dermatoses were noted in 15 control patients under the following therapy: sulfisoxazole (2), insulin (5), and symptomatic therapy (8). The effect of chlorpromazine therapy in combination with sulfisoxazole, insulin, and imipramine was observed in 70 patients. Results showed that a combination of chlorpromazine with sulfisoxazole aggravated the skin condition, whereas a combination with insulin or imipramine improved it. The severity of dermatoses depended on the amount and method of administration of chlorpromazine. Serious cutaneous lesions occurred with injections of 200 to 300 mg of chlorpromazine and with tablets of 400 to 600 mg/day; moderate and slight cases occurred after

injections of up to 125 mg/day. The duration of sunlight exposure was also a determining factor. All of the patients underwent the following treatment: 0.1 g b.i.d. of diphenhydramine, 25 mg b.i.d. of promethazine, and a 10% solution of p.o. or i.v. calcium chloride during a period of 10 to 12 days. After 2 to 3 days of treatment, cutaneous lesions disappeared in all of the patients. Treatment results were equally effective in 15 patients who continued chlorpromazine therapy.

Psychoneurological Hospital
Igren, U.S.S.R.

- 2702 Holler, G. & Menninger-Lerchenthal, E. **Corticosteroidpsychose. Asthma und Geisteskrankheiten. I Mitteilung: V Gesichtspunkt des Nervenarztes.** (Corticosteroid psychosis. Asthma and mental disorders. I. From the viewpoint of the neurologist.) Wiener Zeitschrift für Nervenheilkunde und Deren Grenzgebiete, 20:277-287, 1963.

The case history of a 25-year-old female described. The patient's asthma of 10 years' duration was cured by 5 months' treatment with Decadron (hexadecadrol), consisting of seven 0.5-mg tablets/day for 4 months and one tablet/day during the last month. The onset of a cold at the end of 5 months prompted the patient to take a dose of 5 tablets at one time. This resulted in insomnia and hallucinations, derealization phenomena, and finally an increasing depersonalization. The foregoing were accompanied by anxiety in regard to daily tasks (characteristic of endogenous depression), and acute feelings of inadequacy. The patient was hospitalized because of danger of suicide. After 10 weeks, the disturbances began to resolve. The symptoms that disappeared last were insomnia and feelings of inferiority. The psychic health of the patient was unaffected during mild treatment with hexadecadrol for another 1½ years later. Pathologically, the illness could be best classified with the endocrine psychosyndromes, enabling its explanation as a corticopsychosis. Simultaneous disturbance of the menstrual cycle indicates an impact on the anterior hypophyseal lobe, involvement of the gonads and adrenal cortex. The site of the effect probably is the connection between the hypothalamus and hypophysis. The literature on corticosteroid psychosis is discussed. (43 references.)

Vienna, Austria

2703 Ueda, H., Yamamoto, M., & Kameda, H.
(*Anorexia nervosa*.) Naika, 11:360-
364, 1963.

Anorexia nervosa should be treated by a doctor who has a knowledge of psychiatry or psychology. Four patients with anorexia and four with nervosa symptoms were treated. Diagnoses of this disease should be differentiated from Simmond's disease, diabetes mellitus, malignant disease, or chronic inflammatory diseases, such as tuberculosis and syphilis. Because of complicated symptoms, diagnosis is sometimes difficult. Psychotherapy, chlorpromazine, antidepressants, and insulin shock therapy should be included in the treatment of anorexia nervosa.

Department of Internal Medicine
Tokyo University School of Medicine
Tokyo, Japan

2704 Armed Services Technical Information
Agency. *Emotional stress phenomena
in endocrine function. A report bibliog-
raphy.* Arlington, Virginia, 1957 - 1961,
29 p.

A collection of abstracts of reports concerned with emotional stress phenomena in endocrine function has been presented. The experiments described utilized the pituitary and adrenal glands in order to test their responses to heat, cold, malnutrition, and irradiation.

Defense Documentation Center
Cameron Station
Alexandria, Virginia

2704 Human Factors Research, Incorporated.
A study to determine the effects of
placebos upon performance in a vigilance
task. O'Hanlon, J., Jr., Schmidt, E. A., &
Baker, C. H., Los Angeles, California,
January 1964, 16 p. Contract NONR 4120(00),
unclassified report.

Eighty matched observers, divided into four equal groups, were used in an experiment to study placebo's effect on performance of a conventional vigilance task. Presumably, all observers believed that the placebos had positive, negative, or unknown effects on alertness. The white placebo was alleged to affect performance in an unknown manner; the orange placebo was supposed to make the subjects more alert, and the yellow placebo was supposed to make them less alert. The fourth group took no pills at all. Observers were tested in groups of fours, four groups per day, for 5 days. After administration of the placebo, each observer was given a medical examination to further the deception. Performance was identical in all four conditions. However, the placebos did affect the frequency with which observing responses were made. There was a general decline in performance as time progressed. It was concluded that under the described conditions, placebo does not affect performance.

Human Factors Research, Incorporated
Los Angeles, California

CLINICAL STUDIES

- 2706** Margolin, Solomon. 2. Effects upon physiological systems. b. Nonbarbiturates. In: Root, Walter S. & Hofmann, Frederick G., eds. Physiological pharmacology. A comprehensive treatise. Volume I. The nervous system---Part A. Central nervous system drugs. New York, Academic Press, 1963, p. 239-264.

The nonbarbiturates are divided into two categories, major sedative-hypnotics (chloral hydrate, paraldehyde, methylpentynol, ethinamate, ethchlorvynol, methylprylon, and glutethimide) and minor sedative-hypnotics (bromides, antihistamines, and the opium alkaloids). These drugs are discussed in terms of their effects on the CNS, respiratory system, cardiovascular system, gastrointestinal tract, urogenital tract, and on behavior. The mechanism of action of methylpentynol and of glutethimide is given.

Wallace Laboratories
Cranbury, New Jersey

- 2707** Delay, J., Pichot, P., & Lempérière, T. The therapeutic implications of psilocybin. In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. Hallucinogenic drugs and their psychotherapeutic use. Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. Second session, p. 37-41.

The results of pharmacological and clinical studies of psilocybin are reported. The pharmacological experiments included both in vivo and in vitro studies on mice. The clinical experiments with psilocybin involved the somatic and physiological effects in both normal and psychotic individuals, the psychic effects in normal subjects, and the therapeutic effects in mental patients.

Psychiatric Center
Sainte-Anne
Paris, France

- 2708** Cameron, Kenneth. Some experiences with LSD in the treatment of adolescent boys. In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. Hallucinogenic drugs and their psychotherapeutic use. Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. Fourth session, p. 107-111.

The use of LSD as an adjunct to psychotherapy in the treatment of severe obsessive-compulsive adolescents is described. Eight boys, 14 to 18 years of age, were treated with LSD--psychotherapy sessions. The LSD (40µg) was given i.v., 30 minutes before the psychotherapeutic session. In four cases, LSD was effective; in one case treatment was successful, but LSD did not appear to alter the course of treatment. In one case, LSD complicated therapy, and in two cases, LSD was of no value. In the successful cases, LSD facilitated interviewing, permitted rapid establishment of a therapeutic relationship, and allowed expression of suppressed experience. The drug was not regarded as a substitute for psychotherapy. Five cases, including an additional case of a man in his fifties, reviewed in detail.

Bethelm Royal and Maudsley Hospitals
London, England

- 2709** Leuner, H. Psychotherapy with hallucinogens. A clinical report with special reference to the revival of emotional phases of childhood. In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. Hallucinogenic drugs and their psychotherapeutic use. Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas 1963. Third session, p. 67-73.

The use of hallucinogens (LSD, psilocybin and mescaline) in the psychotherapy of 54 neurotics is reported. Of the 54 cases, showed some degree of improvement. Patients with anxiety neuroses and phobias, chara

neuroses, borderline schizophrenia, puberty neuroses, and reactive depressions responded most favorably to treatment. Little success was observed with cases of sexual neurosis (including homosexuality), conversion hysteria, and infantile personality. A therapeutic factor noted in reviewing these cases, referred to as "revival of emotional phases of childhood," is discussed in detail. Recognition of this factor is essential in the total treatment of the neurotic patient.

Universitäts-Nervenklinik
Höttingen, Germany

2710 Arendsen-Hein, G. W. LSD in the treatment of criminal psychopaths. In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. Hallucinogenic drugs and their psychotherapeutic use. Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. Fourth session, p. 101-106.

The treatment of criminal psychopaths with group LSD sessions is described. Twenty-one subjects in good physical health, with no record of actual psychosis, were selected for treatment. The LSD was given once a week or every 2 weeks, for 10 to 20 weeks, depending on the patients' clinical progress. Dosage was varied according to individual need from 50 μ g to 450 μ g. The patients were treated in groups of five, with one psychiatrist and one nurse in constant attendance. Of the 21 patients, 12 were judged to be clinically improved, and 2 were much improved. One case is reviewed in detail as an illustration of a successful response. The drug appeared to be of definite value in the treatment of psychopaths.

derveen, Holland

2711 Fordham, Michael. Analytic observations on patients using hallucinogenic drugs. In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. Hallucinogenic drugs and their psychotherapeutic use. Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. Fifth session, p. 125-130.

Three cases, two women and one man, in which LSD proved to be detrimental to psychoanalysis are reported. The three

cases illustrate the difficulties inherent in integrating the hallucinatory and other experiences induced by hallucinogens into the ego.

London, England

2712 Rosen, Ismond. Clinical observations on aggression in the treatment of affective disorders with obsessions by the use of lysergic acid and intensive psychotherapy. In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. Hallucinogenic drugs and their psychotherapeutic use. Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. Fifth session, p. 136-140.

The use of LSD in the treatment of two female depressives with obsessional symptoms is described. The first patient, 35 years of age, was given 20 weekly treatments over a period of 8 months and concurrent intensive psychotherapy; LSD dosage ranged from 100 μ g to 250 μ g per session. The second patient, 38 years of age, was given seven LSD sessions. The treatment of both patients was facilitated by LSD, but it was concluded that the ultimate success of the treatment depends on the ability to deal with the analytic transference situation.

British Hospital for
Functional Nervous Disorders
London, England

2713 Sakamoto, T. & Shige, E. (Clinical trials of chlordiazepoxide in laryngopharyngeal paresthesia.) Otolaryngology, 35:585-587, 1963.

Psychotherapy and chlordiazepoxide were used in 32 patients with laryngopharyngeal paresthesia. The effective dosage was approximately 40 to 150 mg/day. The drug was considered to be ineffective if no improvement occurred after a dosage of 200 mg/day. Anorexia occurred in only one case, and symptoms, such as coordination, disturbance, and lethargy, were not observed, probably because the dosage was small (not more than 30 mg/day). However, a patient treated with 20 mg/day chlordiazepoxide for 13 months did not experience side effects. Combined therapy, using chlordiazepoxide with other drugs, also showed an effect in seven cases of laryngopharyngeal paresthesia accompanied by organic diseases. Of the 32

cases treated, 27 showed improvement. In the chlordiazepoxide treatment of the patients with laryngopharyngeal paresthesia, some patients failed to return to the clinic as soon as the symptoms were completely or partially relieved.

Department of Otolaryngology
Hokkaido University School of Medicine
Hokkaido, Japan

- 2714 Shimazono, Y., Nakagawa, S.,
Mashahashi, K., & Michishita, T.
(Clinical experience in chlordiazepoxide.)
Journal of Therapy, 45(4):731-736, 1963.

Chlordiazepoxide was administered to 66 patients who had either various types of neurosis; epilepsy with personality change; schizophrenia with anxiety, restlessness, tension, and obsessive compulsive disorder; cerebral arteriosclerosis; or personality disorders. The results of treatment with chlordiazepoxide were as follows: more than 70% of the psychoneurotic patients showed improvement, especially those with cardio-neurosis, anxiety, neurosis, depressive reaction, tension, and restlessness; epilepsy with personality in epileptic patients with personality changes, some degree of improvement in emotional disorders in the majority of cases was seen, but no remarkable degree of improvement was noted. Symptomatic improvement also occurred in those patients with depressive psychosis and schizophrenia. There were no side effects, except for an occasional case of lethargy or lightheadedness.

Neuropsychiatry Department
Kanazawa University School of Medicine
Kanazawa, Japan

- 2715 Bauer, H. Die Behandlung des schweren Parkinson-Syndroms mit Orphenadrine unter besonderer Berücksichtigung der psychischen Aktivität. (Treatment of severe Parkinson's syndrome with orphenadrine with special reference to mental activity.) Medizinische Klinik, 58(37): 1523-1527, 1963.

Orphenadrine was used in the treatment of 19 hospitalized patients with Parkinson's disease, 11 females and 8 males, 42 to 79 years of age. Daily dosage of orphenadrine

was 225 to 300 mg. Of the 19 patients, 8 improved for at least 4 weeks, 3 showed no change, and 8 regressed with orphenadrine therapy. The effect of the drug on the general condition of the patient, akinesia and handwriting, rigor, tremor, subjective well-being, and drive is discussed, with the incidence of improvement in each area of assessment reported. Side effects were observed in 15 patients during treatment; in 8 cases, orphenadrine had to be discontinued. Side effects included nausea and headache, increase in tremor, and increase in the incidence of oculogyric crisis. It is suggested that orphenadrine be given in combination with other antiparkinsonian agents. Improvement in general condition is determined less by reduction of motor symptoms than by increased drive. The psychic effect of orphenadrine is evident at relatively low doses.

Psychiatric Clinic
Medical Academy
Düsseldorf, Germany

- 2716 Bammer, Hans. ACTH- und Corticoid-behandlung neurologischer Krankheiten (ACTH and corticoid treatment of neurologic diseases.) Deutsche Zeitschrift für Nervenheilkunde, 185:121-149, 1963.

The use of ACTH—corticoid treatment in various neurological diseases is discussed based on clinical trials reported in the literature. Diseases that respond well to this therapy include acute encephalomyelitis, neuromyelitis optica, the Landry form of the acute polyneuritis of Guillain—Barre, trichinosis encephalopathy, delirium tremens, and acute polymyositis. The ACTH—corticoid therapy reduces the incidence of remission in multiple sclerosis, but has little effect on the later course of the disease. In certain neurological diseases, such as myasthenia gravis, the dangers presented by this type of therapy outweigh its advantages.

Neurological Clinic
University of Würzburg
Würzburg, Germany

2717 Leuner, Hanscarl. *Die Psycholytische Therapie: Klinische Psychotherapie mit Hilfe von LSD-25 und verwandten Substanzen.* (Psycholytic therapy: Clinical psychotherapy using LSD-25 and related compounds.) *Zeitschrift für Psychotherapie und Medizinische Psychologie*, 13:57-64, 1963.

Treatment of neuroses by using LSD-25 or psilocybin as an adjunct to psychotherapy is described. Based on a review of over 600 cases treated with LSD-25, psycholytic treatment is recommended in the following disorders: character neuroses, anxiety neuroses and phobias, depressive states (excluding endogenous depressions), perversions and sexual neuroses, compulsive syndromes, and borderline schizophrenia. The following disorders do not respond to LSD: marked hysterical neuroses and hysteria, stuttering neuroses, and marked constitutional infantile personalities. Data on LSD treatment for 74 patients are tabulated: 23 were cured; 28 showed substantial improvement; and 23 showed slight or no improvement. The procedure for LSD and for psilocybin treatment is described. Patients are given a nontoxic dose of the hallucinogen; LSD effects last 6 to 8 hours, and psilocybin effects last 4 to 5 hours. During the dream-like state, a trained psychotherapist interviews the patient. After about 5 hours, the drug session is ended by an injection of a barbiturate. The patients are then assembled in groups of five or six subjects and they express their experiences by painting and sculpting. Another group session is held the following day; one or two individual sessions are held later. The therapeutic phases of the psycholytic experience are discussed, and case histories are given as an illustration of each phase.

University Clinic for
Psychic and Nervous Diseases
Göttingen, Germany

2718 Schneider, Hanns & Prünke, Hanna. *Erfahrungen mit einem barbituratfreien Beruhigungs- und Schlafmittel bei Kindern.* (Experiences with a barbiturate-free sedative and hypnotic in children.) *Deutsches Medizinisches Journal*, 14(11):368-369, 1963.

The nonbarbiturate sedative Centalun (3-methyl-3,4-dihydroxy-4-phenylbutane-1) was tested over a 9-month period in 117 infants and children. A study was done in 35

infants and children to determine the optimum dosage of the drug. In infants $\frac{1}{2}$ to 1 year old, optimum dosage was 15 to 25 mg/kg Centalun; in preschool children, 2 to 6 years of age, 20 to 30 mg/kg; and in school-age children, 7 and above years of age, 10 to 20 mg/kg. The therapeutic dose of Centalun, excluding infants, decreases with increasing age in children. Using the dosages determined in this study, 82 children with various states of unrest and sleep disorders of psychic and organic origin were treated with Centalun. Excellent response was obtained in about 70% of the cases, with a particularly high percentage of good responses in children with brain damage. In the remaining 30% of the cases, a definite sedative effect appeared. Two patients, however, showed no effect at all. Side effects were encountered in only one case—a distinct drop in blood pressure in a 3-year-old child at a dosage of 20 mg/kg.

Children's Hospital
Trier, Germany

2719 Battegay, R. *Vergleichende Bewertung antidepressiv wirksamer Psychopharmaka, unter besonderer Berücksichtigung von Pertofran (Desmethylimipramin).* (Comparative evaluation of antidepressant psychopharmacological agents, with particular reference to Pertofran (desmethylimipramine).) *Nervenarzt*, 34(8):371-373, 1963.

A group of 248 patients with various forms of depression were treated with desmethylimipramine (DMI) to determine indications for the use of this drug. Treatment was begun with injection of 25 to 100 mg DMI daily, in 2 to 4 divided doses. The drug was then given orally in doses of 25 to 200 mg daily. The DMI, in general, produced responses more quickly than did imipramine. In some cases, responses appeared 24 to 48 hours after initiation of therapy; in other cases, therapeutic effect was not apparent until the 8th to 10th day. Of the 248 patients, about 58% responded positively to DMI therapy. Endogenous depression, involutional depression, and depressive states accompanying organic psychotic syndromes reacted best to DMI. In depressions with psychomotor agitation and anxiety, DMI produced either no change or an exacerbation of symptoms. Side effects were

similar to those produced by imipramine, although less intense. No toxic effects were noted.

Psychiatric Clinic
University of Basle
Basle, Switzerland

- 2720** Mallmann-Mühlberger, Elga.
Erfahrungsbericht über die Truxal-Therapie bei 65 Kindern. (Report on experiences with Truxal therapy in 65 children.) *Medizinische Welt*, 28:1455-1458, 1963.

A study was conducted of the effect of chlorprothixene in the treatment of 65 epileptic children, from 2 to 14 years of age, all with pronounced erethism. Fifty-four children had either grand mal, psychomotor, or propulsive petit mal seizures. Duration of therapy ranged from 4 days to 1½ years. The minimum dose of the drug was 5 mg b.i.d., and the maximum dose was 50 mg six times/day. During drug therapy, EEG recordings were made of 39 children. Treatment results were as follows: good results (23), slight and questionable results (25), and no results (16). Five children developed side effects, and eight showed signs of overdosage. No changes due to the drug were observed in the EEG.

Children's Clinic
University of Heidelberg
Heidelberg, Germany

- 2721** Kühns, K. & Simon, M. **Nachuntersuchungen über Verlauf und Prognose der essentiellen Hypertonie bei langfristiger medikamentöser Behandlung.** (Follow-up studies on the course and prognosis of essential hypertension following prolonged drug therapy.) *Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung*, 28: 302-304, 1963.

The effects of drugs, over a period of 10 years, on blood pressure and life expectancy of 4,700 patients with essential hypertension are discussed. The patients were classified according to the following: sex, age groups (up to 39, 40 to 59, and over 60 years), systolic and diastolic blood pressure groups, and hospitalized patients or outpatients. Three subgroups that received only dietary treatment were compared with three subgroups that received

either sedative therapy only, Rauwolfia alkaloids, or mainly hydrazino-phthalazine and ganglioplegics. The relationships between prognosis and sex, age, and systolic and diastolic blood pressure were unaffected by drug therapy in the untreated hypertensive patients. The blood pressure of drug-treated outpatients at rest did not differ significantly from the spontaneous course of blood pressure of patients who were on the dietary regimen only. However the life expectancy of drug-treated hypertensive patients is greater in comparison with that of hypertensive patients who did not receive drugs. The Rauwolfia alkaloid had a pronounced favorable effect on life expectancy. Mortality in the hypertensive patients was especially high in males between the ages of 45 and 70 years.

Medical Clinic
University of Göttingen
Göttingen, Germany

- 2722** van Praag, H. M. & Leijuse, B.
Psychiatric Department and Biochemical Laboratory of the Hospital Dijkzigt, Rotterdam, The Netherlands. The meaning of monoaminoxidase inhibition as antidepressant principle. (Staff document). 1963, 6 p. Typed.

The effects of MAO inhibitors and EST on the metabolism of endogenous serotonin in depressed patients were investigated. Eleven patients (4 men and 7 women, 24 to 76 years of age) with diagnoses of melancholic depression (4 patients), neurotic depression (2), psychogenic depression (2), involutional depression (1), and organic depression (2) were given iproniazid (100 mg/day). Another group of 12 patients (3 men and 9 women, 20 to 74 years of age) with diagnoses of melancholic depression (3 patients), neurotic depression (3), psychogenic depression (3), involutional depression (1), and organic depression (2) were given isocarboxazid (40 mg/day). The metabolism of endogenous serotonin, evaluated 2 to 3 times/week 2 weeks before and after the treatment and during the 6 weeks of treatment, was measured by paper chromatographic determination of the 24-hour excretion of 5-hydroxyindoleacetic acid (5HIAA). During the 6 weeks of treatment patients (7 on iproniazid and 6 on isocarboxazid) showed considerable improvement. The average 24-hour excretion of 5HIAA for the improved cases before the treatment was significantly lower than for the 10

unimproved cases. During the treatment, the 5HIAA excretion of the 13 improved cases increased gradually, starting during the second week of treatment in the iproniazid group and during the third week of treatment in the isocarboxazid group. The first clinical signs of recovery appeared at 12 and 14 days, respectively; therefore, there was good conformity between the appearance of psychic and biochemical phenomena. Six of the patients, with little reaction to the 10 inhibitors, underwent EST. The results of the shock treatment, except for one patient, was excellent; the 5HIAA excretion was not influenced. The urine of two of the patients was collected 24 hours before and after the first and seventh shock. No fluctuations of 5HIAA excretion occurred during this period.

Psychiatric Hospital and
Biochemical Laboratory
Rijksgesticht Hospital
Amsterdam, The Netherlands

23 Galenko, V. Ye. & Kuznetsov, O. N.
O primeneni etaperazina pri lechenii
schizofrenii. (On the use of Etaperazine in
the treatment of schizophrenia.) Journal of
Neuropathology and Psychiatry, 63(1):80-86,
1963.

In order to study its therapeutic efficacy, perphenazine was administered to 63 patients (7 to 55 years of age), of whom 58 were men. There were 36 paranoids, 10 catatonics, 5 simple schizophrenics, and 12 periodic schizophrenics. The initial dosage of perphenazine administered to patients who had never been treated with neuroleptics was 36 to 72 mg/day. Patients who had demonstrated a particular resistance to chlorpromazine were started on a dosage of 36 to 72 mg perphenazine daily. The most effective doses were as follows: for previously treated patients, 36 to 72 mg/day; for catatonic patients, 100 mg/day or more; and for cases resisting all types of therapy, up to 300 mg/day. The individual optimal doses were continued for 1-1/2 weeks to 3 months. Maintenance dosage of 6 to 72 mg/day was continued for 1-1/2 to 10 months. The most significant effect was achieved in the treatment of patients who were suffering from periodic schizophrenia; 20 cures were effected. The preparation was also effective in treating patients who had previously received chlorpromazine. Of 31 patients who had been particularly resistant to chlorpromazine, 11 were significantly improved, and another 11 were moderately improved by

the administration of perphenazine. The drug was not satisfactory in the treatment of catatonia. The main side effect was the development of Parkinson's syndrome, which appeared in 32 patients. Perphenazine was well-tolerated by all the patients.

Moscow, U.S.S.R.

2724 Avrutskiy, G. Ya., Gurovich, I. Ya.,
& Aleksandrovskiy, Yu. A. Lecheniye
schizofrenii galoanizonom (20-28 MD).
(Treatment of schizophrenia with
haloanisone (20-28 MD).) Journal of
Neuropathology and Psychiatry, 63(1):87-91,
1963.

The efficacy of haloanisone, a new preparation of the butyrophenone class, was determined in the treatment of schizophrenia in 36 patients. Of these, 20 were suffering from paranoid schizophrenia and 12 were catatonic. On the initiation of treatment, haloanisone was administered in 20-mg doses i.m., two to three times an hour. This dosage was increased to 100 to 120 mg an hour, and especially resistant cases received 160 to 180 mg. In five such cases, the action of the preparation was strengthened by combining the dosage with chlorpromazine. Treatment was continued for a 2- to 3-month period in order to determine the effects of the preparation on psychomotor excitation. In a majority of patients, akathisia, taxikinesia, and parkinsonism were observed. The effect of the treatment depended directly upon the type of motor excitation involved. The drug proved most effective in the treatment of periodic schizophrenia and oneiro-catatonia. Motor excitation was relieved and patients returned to a state of relative calmness. However, they continued to manifest emotional fantasies, for example, delusions of space-flight and of being in another world. In cases of paranoia, progress was somewhat slower at the outset, and was also accompanied by the disappearance of hallucinations. Haloanisone proved most effective in the treatment of paranoid schizophrenia (its action occurred more rapidly than chlorpromazine), and was especially beneficial to patients suffering from oneiro-catatonia. The authors conclude that the preparation will prove effective in the treatment of motor excitation in patients who have displayed particular resistance to other forms of therapy.

Moscow, U.S.S.R.

2725 Schanz, Gerhard. Zur Anwendung des Schlaf- und Beruhigungsmittels Centalun. Therapeutische Ergebnisse aus der Frauenklinik. (On the use of the sedative and tranquilizing agent Centalun. Therapeutic results in a woman's hospital.) Medizinische Monatsschrift, 17(5):309-310, 1963.

Centalun (3-methyl-3,4-dihydroxy-4-phenylbutine-1) was tested in 400 female patients with sleep disorders of various etiology over a 1-year period. The drug induced sleep within 15 to 30 minutes; duration of sleep was 3 to 6 hours. Patients were not groggy when awakened for medication during the night, and falling asleep again was not hindered by the drug. The drug produced no morning hangovers. Most sleep disorders responded to doses of 250 to 500 mg Centalun. Older patients and patients long confined to bed often needed 500 to 750 mg. In severe sleep disorders, Centalun was combined with a small dose of a phenothiazine. Psychoneurotic patients given 250 mg Centalun t.i.d. or q.i.d. did not require additional psychopharmacological agents for calming effect. No side effects were noted. The drug was safely combined with analgesics and spasmolytics. A cumulative effect was noted in Centalun's hypnotic and sedative properties when it was combined with barbiturates and phenothiazines.

Woman's Clinic
St. Marien Hospital
Ludwigshafen, Germany

2726 Friederichs, P. Meine Erfahrungen mit dem Schlafmittel Centalun in einem Alters- und Pflegeheim. (My experiences with the sedative Centalun in a nursing home and home for the aged.) Medizinische Monatsschrift, 17(5):310-311, 1963.

Centalun (3-methyl-3,4-dihydroxy-4-phenylbutine-1) was tested for its hypnotic effect on geriatric patients in short-term and long-term studies. In the short-term study, 17 female and 6 male geriatric patients, average age 65 years, who suffered from restlessness and sleep disorders, were given Centalun for 17 days. The drug was effective in 19 patients and had no effect in 4. Doses of 500 mg/day produced a good hypnotic effect in nonpsychiatric patients. In psychiatric patients, Centalun, in doses of 300 to 3,000 mg/day, was effective when combined with other psychopharmacological drugs. The only side effect was headache

in one patient. In the long-term study, 18 geriatric patients were given Centalun (500 to 1,000 mg) each evening for 7 months. The drug produced adequate sedation in all patients except those patients that were subject to pain. A dose of 600 mg of the drug was adequate for depressed patients. Patients with severe cardiac decompensation phenomena showed good tolerance.

Federal Nursing Home and Home for the Aged
Heidesheim, Germany

2727 von Schumann, Hans-Joachim. Insidon bei psychosomatischen Erkrankungen in Klinik und Praxis. Die Beziehung zwischen Psyche und Soma. (Insidon in psychosomatic diseases in clinical and private practice. The relation between psyche and soma.) Medizinische Monatsschrift, 17(7):434-436, 1963.

Inpatients (52) and outpatients (120) with psychosomatic symptoms were treated with a combination of psychotherapy and opipramol. Opipramol was administered, as a rule, to hospital patients in a divided dosage of 300 mg/day and to outpatients in a divided dosage of 150 mg/day. The biphasic effect of initial calming, which changed into increased psychic drive after 5 to 10 days facilitated psychotherapy. The therapeutic effect appeared within 3 to 24 hours. The target symptoms disappeared in 42 of the 52 inpatients and in 78 of the 120 outpatients. Eight of the hospitalized patients were improved, and 28 of the outpatients showed improvement; the rest were unchanged. Two case histories are discussed in detail.

Private Clinic for Psychotherapy
Dusseldorf, Germany

2728 Koch, Ludwig. Klinische Erfahrungen mit Centalun, einem neuen sedativ-hypnotischen Präparat. (Clinical experiences with Centalun, a new hypnotic-sedative preparation.) Münchener Medizinische Wochenschrift, 105:1273-1275, 1963.

Over a period of 7 months, Centalun (3-methyl-3,4-dihydroxy-4-phenylbutine-1) was used to treat 160 female patients, 20 to 85 years of age, with the following diagnoses: hebephrenia, erethistic feeble-mindedness, paranoia, agitated endogenous

and reactive exogenous depression, delirium accompanying arteriosclerosis, general unrest, and sleep disorders. When given as sedative, dosage was generally 0.9 to 1.2 g daily, divided into three or four doses. The patients were calm, but remained awake and alert. Alcoholic withdrawal symptoms were suppressed with doses of 0.5 b.i.d. to t.i.d. Patients with agitated depression pretreated with phenothiazines and an MAO inhibitor were sedated at doses of 3.0 to 4.0 g daily. Hypnotic doses ranged from 1.0 to 4.5 g. Sleep occurred within 30 minutes of Centalun administration, and lasted 4 to 5 hours. No hangover was noted at any dosage level. The drug produced no toxic effects, and could be given safely in combination with phenothiazines, paraldehydes, and barbiturates.

Psychiatric Hospital
Munich, Germany

2729 Jantzen, Heinz. Beitrag zur Muskelrelaxation und Psycho sedation ab partu. Erfahrungen mit Diazepin-Präparaten-Tokographische Untersuchungen. Contribution to the use of muscle relaxants and psychosedatives in childbirth. Clinical trial of diazepam preparations and tocographic studies.) Munchener Medizinische Wochenschrift, 105(27):1397-1399, 1963.

The psychorelaxant properties of chlordiazepoxide and diazepam were tested on women during childbirth. Chlordiazepoxide was tested on 250 women, including 100 imiparas, in doses of 50 mg and of 100 to 200 mg. The lower dose produced good to very good results in 37% of the cases. The higher dose produced excellent results in 63% of the cases. Ninety-two women were also given 50 to 200 mg pethidine HCl as an analgesic. Chlordiazepoxide potentiated the pethidine effect, producing greater analgesia than pethidine alone. Side effects with chlordiazepoxide included three cases of depression of labor. Diazepam was given to 50 women in doses of 10 to 20 mg i.m. or i.v.; i.v. administration resulted in twilight sleep, and i.m. administration eliminated tension and anxiety. In combination with pethidine, the effect was similar to that produced by a psychic cocktail. No side effects were noted with diazepam.

Women's Clinic
City Hospital
Frankfurt-am-Main, Germany

2730 Shchelkunov, Ye. L. Farmakologicheskoye obosnovaniye primeneniya otechestvennogo preparata khloratsizina v kachestve antidepressanta. (Pharmacological assessment of the antidepressive action of the Soviet preparation chloracizine.) Zhurnal Nevropatologii i Psikhatrii imeni S.S. Korsakova, 63:1415-1419, 1963.

Chloracizine produces an increase in the volumetric velocity of coronary blood flow, and also forestalls certain forms of arrhythmias. In clinics, the preparation is used often in treating coronary illnesses. It has been shown that there is a two-sided reaction between chlorpromazine and amphetamine on conditioned reflexes; chloracizine on the other hand, has a very definite ability to strengthen amphetamine's central action. In the assessment of chloracizine, a comparative approach was employed, using chloracizine and the antidepressant imipramine. The study showed that imipramine, as well as chloracizine, increases the capacity of amphetamine to produce disorders of the conditioned reflexes in laboratory rats. It was found that chloracizine in doses of 1 to 10 mg/kg significantly increases the toxicity of amphetamine, very sharply increasing its lethal and motor-excitation effects. The action of chloracizine is qualitatively similar to imipramine, but it is differentiated by an appreciably greater strength, and when the dosage of chloracizine was increased to 50 mg/kg, its stimulating action did not replace a protective one, which did occur with imipramine. Chloracizine was found to be more effective than imipramine when administered in equal doses of 5 mg/kg, and it was also more effective than the standard dose of amphetamine (1 mg/kg). This study confirms the assumption that the adreno-positive action of chloracizine is considerable in the case of "simple" depressions.

Scientific Research Institute for
Psychoneurology
Psychopharmacology Laboratory
Leningrad, U.S.S.R.

2731 Mosketi, K. V., Bel'skaya, G. M. & Muratova, I. D. Opyt primeneniya iodistogo litiya dlya lecheniya nekotorykh psikhoticheskikh sostoyaniy. (Experience in the use of lithium iodide in the treatment of some psychotic states.) Zhurnal Nevropatologii i Psikhatrii imeni S.S. Korsakova 63(1):92-95, 1963.

A clinical study was conducted on the effect of lithium iodide in the treatment of 127 patients with psychic disorders, 83

men and 44 women, whose ages ranged from 18 to 59 years. The duration of illness ranged from several days to several decades. The psychic disorders were as follows: schizophrenia (56 patients), vascular psychosis (27), organic psychosis (10), presenile psychosis (7), toxic psychosis (9), somatogenic psychosis (4), epilepsy (9), manic depressive (3), and neurotic reaction (2). Each patient received a 10% solution of lithium iodide i.v. in daily doses of 5.0 to 10.0 ml. The patients were also given chlorpromazine and hypoglycemic doses of insulin. The course of treatment consisted of 7 to 15 infusions. Treatment results were as follows: good improvement (44 patients), insignificant improvement (39), and no improvement (44). There were no serious side effects. During the fourth and fifth days of treatment, 19 women exhibited general weakness, hypotension, and slight dizziness; blood changes, as observed by an acceleration of the erythrocyte sedimentation reaction, were noted in 8 patients. The solution proved most effective in the treatment of patients suffering from hallucinatory and depressive paranoia.

The Psychiatric Faculty
Arkhangelsk Medical Institute
Arkhangelsk, U.S.S.R.

- 2732** Pennington, Veronica M. **A study to determine possible differences in the formed blood elements of normal and schizophrenic subjects.** *Journal of Neuropsychiatry*, 5(1):21-27, 1963.

Based on findings by Dr. Harry Vander Kamp that in the schizophrenic patient the nucleus of the lymphocytes stained black and the nuclear material was fragmented, and that similar differences exist in the granulocytes, several blood samples of 32 patients with schizophrenic reactions, 12 with other diagnoses, and 5 normals were stained with the Masson-Trichrome stain, and the blood of 17 schizophrenic patients was stained with Wright's stain. In addition, the blood of five schizophrenic patients not on phenothiazines, five on phenothiazines, and one normal was prepared for electron microscopy. To eliminate the possibility that staining differences were due to phenothiazine medication, blood samples of schizophrenic patients were taken before and following medication. The blood samples were studied by several doctors who were not able to duplicate Dr. Vander Kamp's findings. By use of electron microscopy, some positive findings were obtained in one

schizophrenic patient. The blood of 82 schizophrenic patients was examined with light microscopy, and disorganized and unpatterned nuclear material concentrated at the nucleus was found. Plates are included as illustrations. More extensive work is needed to make the formed elements of the blood confirmatory of schizophrenic reaction.

Psychiatric Service
Veterans Administration Center
Jackson, Mississippi

- 2733** Gibbs, Frederic A. & Gibbs, Erna L. **The mitten pattern. An electroencephalographic abnormality correlating with psychosis.** *Journal of Neuropsychiatry*, 5(1):6-13, 1963.

The EEG "mitten" pattern seen in adult psychotics and parkinsonian patients is described. This pattern does not repeat rhythmically and occurs only in sleep. The mitten patterns are divided into two types—those with a fast component with a duration of 1/10 to 1/12 second (B mitten) and those with a fast component slower than 1/10 second (A mitten). The A mitten correlates with parkinsonism and the B mitten with psychosis. The presence of a mitten pattern in the EEG does not provide direct evidence of psychiatric disorder, but it does provide clues to the location and character of the disorder.

University of Illinois
College of Medicine
Chicago, Illinois

- 2734** Wapner, Seymour & Krus, Donald M. **Effects of lysergic acid diethylamide, and differences between normals and schizophrenics on the Stroop Color-Word Test.** *Journal of Neuropsychiatry*, 2:76-8, 1960.

The performance of normal adults and of schizophrenics on the Stroop Color-Word Test under LSD and under placebo was compared. The subject sample included 24 normal adults, 12 males and 12 females, 22 to 57 years of age (mean age, 30 years) and 24 adult chronic schizophrenics, 12 males and 12 females, 22 to 56 years of age (mean age, 40 years). On each of two test days subjects were given 2 cc of a tasteless,

colorless liquid, 2 to 3 hours before testing. On the drug day, the liquid consisted of water plus 75 μ g LSD. On placebo, schizophrenics performed more slowly than did normals on all three phases of the Stroop Color-Word Test; the schizophrenics were differentially slower on the third phase (capacity to maintain a course of action independent of intrusion by competing stimuli) than were normals. Under LSD, overall performance is slowed for both schizophrenic and normal subjects. Both schizophrenics and normals are differentially slower on the third phase.

Clark University
Worcester, Massachusetts

2735 Kamp, Harry Vander. **Prognostic determinants in schizophrenia.** *Journal of Neuropsychiatry*, 5(1):118-122, 1963.

Patients hospitalized for schizophrenic reaction show marked individual differences. The variation in length of required hospitalization reflects basic neurophysiologic differences. Studies have been made in which the delicately balanced functioning of the autonomic nervous system was deliberately disturbed. By disturbing the homeostasis of the autonomic nervous system with a pharmacologic stress, neurophysiologic differences can be demonstrated. Methacholine, 10 mg i.m., was given to schizophrenic patients as a prognostic test in evaluating autonomic response and global reactivity. There was good correlation between the global reactivity ratings and the duration of hospitalization. The variation in response is due in part to abnormal methylation in the metabolic sequence of DOPA to epinephrine. Prognosis in schizophrenia thus depends on the adjustment the organism can make to formation and concentration of normal and abnormal metabolites in response to stress.

Veterans Administration Hospital
Battle Creek, Michigan

2736 Gomirato, G. & Hydn, H. A **biochemical glia error in the Parkinson disease.** *Brain*, 86:773-780, 1963.

Biopsies of globus pallidus were performed in 7 Parkinson patients (5 men and 2 women, ages 38 to 58 years) in order to determine the role of the glia in Parkinson's disease.

Three of the cases had received no therapy before death, two cases had received small doses of benzhexol for a 2-year period before death, and one case had received scopolamine and atropine for 5 years, but only benzhexol for the 5-year period preceding death. The control cases were four persons (52 to 70 years of age) who had died suddenly and had no history of neurological, psychiatric, or circulatory diseases. In pronounced cases of Parkinson's disease, increased amounts of RNA were found in both glia and neurons. The glial RNA base composition was markedly altered, with increased adenine and decreased guanine and uracil values. The nerve cell RNA showed less pronounced changes. Bilateral RNA analyses of one case permitted a timing and correlation of biochemical and clinical findings. It was concluded that in the glia-neuron-effector organ, the primary biochemical error of the glia in Parkinson's disease secondarily affects the RNA synthesis of the neuron, manifesting itself in muscle tremor and rigidity.

University of Pisa
Pisa, Italy

2737 Courchet, J. L. & Christodoulou, G. **Perfusions intraveineuses glucosées isotoniques en psychiatrie. (Aperçu clinique et pathogénique à propos de 150 cas hospitaliers). (Intravenous perfusions of isotonic glucose in psychiatry. (Clinical and pathogenetic observations in connection with hospitalized cases).)** *Service de Neuro-Psychiatrie, Hôpital de Melun*, 39(51):2450-2458, 1963.

A clinical study has demonstrated that certain acute psychoses can be cured by i.v. perfusions (polyvitaminized) of isotonic glucose. Between 1960 and 1962, observations were made of 147 hospital patients, 100 having acute psychoses, who received slow i.v. perfusions of isotonic glucose (dosage 100 to 200 cc) and vitamin B. The exclusive use of these perfusions resulted in the cure of 104 patients, 88 of whom were acute cases. In half of the cases, each required less than 10 perfusions, and less than 20 perfusions were needed for each of the remaining patients. Recoveries were complete, and with very few exceptions, no relapses were noted over a 2-year period. The acute psychoses treated included mental confusion, severe hallucinatory delirium, mania, depressive states, related syndromes, and complications. A biological study of 38 experimental cases established that the

cure resulting from isotonic glucose perfusions alone is significantly related to the action of the perfusions on the movement of potassium in the organism, although this element is not part of the perfusion. Several hypotheses are presented concerning the action of potassium on the nervous cell.

Neuropsychiatric Clinic
Hôpital de Melun
Paris, France

- 2738** Plante, Normand. Un tranquillisant anxiolytique et hypnotique. (An anxiolytic and hypnotic tranquilizer.) Laval Medical, 34(8):969-973, 1963.

A clinical trial of ethylisobutrazine, an amine derivative of phenothiazine, was conducted to establish its optimum dosage, possible side effects, and efficacy and to establish the clinical response of various diagnostic categories. Fifty-three male mental patients (18 to 57 years of age), who had been hospitalized from 2 months to 10 years, were selected because of their poor response to other drug therapy. Thirty patients had the following types of schizophrenia: 18 hebephrenic, 5 hebephrenic-catatonic, 4 paranoiac, 1 acute schizophrenic, 1 paranoiac-hypochondriac, and 1 schizoaffective psychotic. After ethylisobutrazine, complete remission occurred in 12 patients, 10 experienced remission of mental aberrations and were capable of self-criticism, 5 had reduced primary and secondary symptoms and began to participate in hospital activities, and 3 were unchanged. Twenty-three patients were in the nonschizophrenic group; diagnostic groups included 10 manic-depressives, 4 patients with alcoholic toxicomania, 2 psychopaths, 1 patient with mixed psychoneurosis, 1 epileptic with mental deficiency, 1 epileptic with accompanying psychosis, and 4 psychotics with mental deficiency. Excellent or good results were obtained in the majority of the patients after ethylisobutrazine therapy. The drug was given in 10-mg tablets, with an initial dose of one tablet at meals and two at bedtime. The highest dosage was 250 mg/day, but doses usually varied from 30 to 150 mg/day. All laboratory tests were normal. Four patients experienced asthenia, sleepiness, or motor symptoms. Extrapyramidal symptoms were almost totally absent even at the maximal 250-mg dose. Slight vasodilation of the face and weight changes were noted. The drug acted as a powerful tranquilizer and antianxiety agent, with secondary sedative effects. Ethylisobutrazine was concluded to be a valuable

adjunct in psychotherapy and in the rehabilitation of both schizophrenics and nonschizophrenic psychotics tested.

(No address)

- 2739** Laborit, G., Larcan, A., & Kind, A. Etude électrocardiographique du 4-hydroxybutyrate de Na. (Electrocardiographic study of sodium 4-hydroxybutyrate.) Agressologie, 4(1):77-88, 1963.

The ECG records of 47 neurosurgical patients, 10 to 71 years of age, anesthetized with sodium-4-hydroxybutyrate were studied. Eight patients showed ECG abnormalities before anesthesia and the remaining patients showed normal ECG's. Operations were performed on thirty-six patients under normal temperature and on 11 patients under moderate hypothermia. The eight patients with abnormal ECG's showed no anomaly due to sodium-4-hydroxybutyrate and no modification of previous tracings. The subjects who initially had normal ECG's showed occasional slight anomalies. Normal patients who were under hypothermia showed definite ECG anomalies.

Neurosurgical Department
Lariboisière Hospital
Paris, France

- 2740** Jacquiel, Gilberte, Robert, G., & Morel, J. La centrophénoxine dans le traitement des syndromes confusionnels et de déficit intellectuel. (Centrophenoxine in the treatment of confusional syndromes and intellectual deficiency.) Presse Médicale, 71(18):919-920, 1963.

A clinical study of the effects of centrophenoxine on 29 mentally disturbed patients revealed that this drug produced generally excellent results, particularly in cases of confusion syndromes. The 29 cases studied included 15 cases of mental confusion following delirium tremens, 4 cases of intellectual impairment due to alcoholism, 6 cases of senile dementia, 2 cases of cerebral atrophy, 1 case of general paralysis, and 1 case of encephalitic coma. The drug was administered by i.v. or i.m. injections of 1 to 1.5 g in severe cases, the most frequent and average dose being from 300 to 600 mg/day. The 600-mg dose produced the most rapid results. The case histories of 10 male patients, 23 to 70 years of age, are discussed individually.

ven during a lengthy period of treatment, there was a total absence of toxicity, and there were no deleterious side effects. All cases of mental confusion following delirium tremens were cured. Results were very good in two cases of intellectual impairment due to alcoholism, and two other cases improved sufficiently to permit discharge. Only one case of senile dementia improved slightly, whereas both cases of cerebral atrophy showed good results and a symptomatic improvement. Both general paralysis and encephalitic coma reacted favorably to this treatment.

ençon, France

41 Ey, Henri, Cor-Mordret, M., & Eppe, J.-P. *Sur le traitement des psychoses chroniques par la trifluoperazine.* (Treatment of chronic psychoses with the use of trifluoperazine.) *Evolution psychiatrique*, 27:399-411, 1963.

trifluoperazine was tested in the treatment of 30 chronic psychotics (20 with schizophrenia, 2 with chronic hallucinatory psychoses, 5 with paranoia, and 3 with delirium), 26 of whom had proved refractory to extremely varied psychiatric therapy. Dosage was increased from an initial 10 mg daily to 30 or 50 mg daily; maintenance dosage was 10 or 5 mg daily. Of the 30 patients, 13 showed improvement; the first signs of improvement were usually noted about the ninth day of treatment. The paranoid and hebephrenic—catatonic forms of schizophrenia, chronic hallucinatory psychoses, and delirium responded well to trifluoperazine; patients with simple schizophrenia showed no benefit. The drug rapidly eliminated delirium, but had no effect on anxiety, thus necessitating combined medication with chlorthalidopoxide or meprobamate, or with ECT. Side effects included an akinetic—hypertonic syndrome in 4 patients, tremor of hands and arms in 4, severe paresthesia in 4, akathisia with choreiform movements in 7, parkinsonian syndrome in 1, asthenia in 11, sleep disorders in one-fifth of the patient sample, and facial edema in 2. Sleep disorders that appeared at the outset of therapy indicated a poor prognosis for trifluoperazine therapy. There was no parallel between the intensity of extrapyramidal disorders and therapeutic results.

o address)

2742 Thoulon, J.-M. & Theoleyre, J.

Utilisation de la propyromazine au cours de l'accouchement dirigé. (Use of propyromazine in the course of directed labor.) *Lyon Medical*, 210:511-530, 1963.

As part of a study on new antispasmodics in obstetrics, during 2 months, 165 maternity cases requiring a therapeutic antispasmodic were given propyromazine, and uterine contractions were studied clinically, as well as with a Lorand tocograph. Ninety-two multiparas and 73 primiparas received the drug; it was administered during different stages of labor to analyze its time effects. Propyromazine was administered i.v. in a 20-mg dose, which was often given more than once. In two cases, 40 mg was administered in one dose. Its action on dilation and uterine contractions, on the expulsive phase and delivery, its retention in the newborn, and its maternal retention and subsequent development were studied. Numerous case histories are given. When given for arrhythmic contractions with no dilation, in both primiparas and multiparas, it arrested contractions and pain sensations for 8 hours, followed by a resumption of regular contractions. When dilation had already begun, propyromazine regularized the time and spacing of uterine contractions and produced coordination between deep contractions and cervical dilation. No serious cases of hemorrhage were observed, even when the drug was administered less than an hour before delivery. Propyromazine was most effective in relaxing a rigid cervix and in reducing edema. No unfavorable drug effects were noted during delivery. All newborns were rated on the Apgar scale: 43 scored 10; 8 scored 9; 5 scored 8; 3 scored 7; 1 scored 6; 1 died before delivery; and 1 had a hemolytic abnormality requiring immediate transfusions. No side effects were observed in the newborn, even when the drug was administered in an advanced stage of dilation.

Obstetrical Clinic
Lyon, France

2743 Body, C. *Utilisation d'un substitut de l'atropine en anesthésiologie, la propyromazine: A propos de 544 cas.* (Use of an atropine substitute in anesthesiology, propyromazine: A propos of 544 cases.) *Anesthesia and Analgesia*, 20:641-647, 1963.

The use of the atropine substitute propyromazine as an anesthetic premedication in 544 surgical cases is discussed. Most of

the patients were adults, but about 100 of the cases were children. Propyromazine premedication was almost always given in conjunction with promethazine and pethidine. In adults, the standard dose was 20 mg propyromazine, plus the other drugs, injected i.m. about 40 minutes before anesthesia. In children, the dose varied with age at the rate of 0.5 to 1 mg/kg, but never exceeded 20 mg. Propyromazine was used alone in certain cases, notably cesareans. In the majority of cases, the premedication was judged to be better than atropine, although the timing was found to be important. Narcosis was induced in the classical manner, respiratory spasm was never observed, and bronchial hypersecretion in thoracic surgery appeared to be diminished. Hiccups occurred in seven cases, and vagal bradycardia with lowered pulse, and marked hypotension occurred in three. Premedication with propyromazine produced nausea in only 4% of the patients and vomiting in only 10%. Six of the hiccup cases responded to a single dose of 20 mg propyromazine i.v., and hyperventilation in the seventh case responded to a second injection of the drug. The three bradycardia cases also responded immediately to 20 mg i.v. Postoperatively, propyromazine was useful for hiccups, and for colic and digestive spasms.

Thoracic Surgery Division
Pontchaillou Hospital
Rennes, France

- 2744 Friedman, Henry T. **Librium-theophylline-ephedrine compound in bronchial asthma. A double blind study in 100 patients.** *Annals of Allergy*, 21:163-167, 1963.

A chlordiazepoxide—ephedrine—theophylline preparation was tested in a blind cross-over study for the treatment of 100 asthmatics (51 females and 49 males, with an age range of 1 to 70 years). Two kinds of tablets were given: one contained 10 mg chlordiazepoxide, 130 mg theophylline, and 24 mg ephedrine HCl; and the other, the conventional asthma treatment, had 8 mg phenobarbital in lieu of the tranquilizer and the same quantities of the other two components. Seven case histories are given to illustrate various responses to the two drug combinations. The phenobarbital mixture was effective in 94 patients, and the chlordiazepoxide mixture was effective in 91 patients. Except in isolated cases, there was little variation in the rate of onset of improvement

and the duration of effectiveness. Marked differences in the side effects produced by the two mixtures were observed. The chlordiazepoxide mixture produced side effects in 14 patients, but the phenobarbital mixture produced side effects in 73 patients. The chlordiazepoxide mixture was concluded to be a valuable therapeutic agent in the treatment of asthma.

435 North Roxbury Drive
Beverly Hills, California

- 2745 Kutin, V. P. **0 vozmozhnostyakh sochetannogo primeneniya insulina i aminazina dlya lecheniya bol'nykh schizofreniyey. Soobshcheniye pyervoye. (On the potentialities of the combined use of insulin and chlorpromazine in the treatment of schizophrenic patients. Part I.)** *Journal of Neuropathology and Psychiatry*, 63(1):114-118, 1963.

Due to contradictory evidence in existing literature on the hyperglycemic and convulsion-inducing effects of a combination of insulin therapy and chlorpromazine therapy in schizophrenia, both drugs were administered to 20 schizophrenic patients, none of whom were suffering from any other somatic illness. Of those treated, seven were under 20 years of age, nine were between 20 and 30, and four were between 30 and 40. Duration of illness ranged from under 1 year to over 5 years (mean, 1 to 3 years). Each patient was given chlorpromazine i.m. in daily increasing doses of 0.025, 0.05, 0.075, 0.1, 0.125, and 0.15 g, followed 1 hour later by 20 units of insulin. The effect on blood sugar was then studied at intervals of 1, 2, 3, and 4 hours. Three cases are discussed in detail. The studies demonstrated that the reaction in each patient was dependent directly upon the amount of chlorpromazine. Individually optimal doses of chlorpromazine pretreatment can reduce the coma-producing dose of insulin by 30% to 40%, and assure absence of violent psychomotor excitation. The combination treatment effected beneficial results in those patients for whom neither insulin nor chlorpromazine therapy had produced significant results. In the majority of cases, improvement did not occur immediately, but took place over the course of 1 or 2 months.

Zhitomir Oblast Psychoneurological Hospital
Zhitomir, U.S.S.R.

2746 Janata, J. & Danninger, F. K
analgetickému účinku fenothiazinových
preparátů při umělém přerušení těhotenství.
On the analgesic value of phenothiazine
preparation in abortion.) Ceskoslovenska
ginekologie, 28(3):186-187, 1963.

In order to determine the analgesic effects
of phenothiazine preparations, 8 primiparas
and 86 multiparas in abortion were given the
following drugs: 60 received injections of
100 mg of pethidine plus 50 mg of chlor-
promazine; 21 were given 100 mg of pethidine
plus 50 mg of phenegan (Promethazine); 6
were given 100 mg of pethidine plus 50 mg of
phenegan (Atosil); and 7 were given an
11 preparation. The drugs were diluted to
10 ml and injected i.v. over a period of
10 to 7 minutes, 10 to 20 minutes before the
operation. The analgesic effects were
excellent in 2 patients, very good in 5,
good in 26, slight in 44, and inadequate in
1. The i.v. administration of pethidine
with neuroplegics resulted in great muscular
weakness and difficulty in speaking. The
patients reported that they had strong pain
sensations during the operations, but
because of weakness, they could not make
vocal sounds. Of all the patients, 93%
reported feeling pain during the operations
and remembered it later; thus, amnesia to
pain was not achieved. Although these drug
combinations are advantageous in regard to
facilitating dilatation and reducing blood
loss, because of their weak analgesic action
they are recommended for use only in cases
in which thiopental or total narcosis are
contraindicated.

Gynecological-Obstetric Ward
State Hospital
Přerov, Czechoslovakia

2747 Suwa, N. (Clinical trials with
thioridazine in schizophrenia.)
Journal of Therapy, 45(7):1293-1299, 1963.

The effects of thioridazine in the treatment
of 12 schizophrenics are reported. The
initial dosage was 100 to 300 mg/day,
increasing to 800 to 1,200 mg/day. The
maintenance dose was 300 mg/day or according
to need. No unusual side effects were noted
at the prescribed doses. However, when
the dose was increased to 700 to 1,000 mg/
day, mild parkinsonian symptoms were
observed in two cases. In the early stage
of treatment, the psychomotor suppressive
effect of thioridazine was relatively
mild and appeared later than did that of
lorpromazine. As compared with other
phenothiazine derivatives, thioridazine is

similar to pecazine. However, thioridazine
is considered to be superior because of its
few side effects and its stronger sedative
effect. Thioridazine is considered an
effective drug in the treatment of psychi-
atric disorders.

Department of Neuropsychiatry
Hokkaido University School of Medicine
Hokkaido, Japan

2748 Sternberg, E. Y. & Smoulevitch, A. B.
Opyt primeneniya neyrolepticheskikh
sredstv pri khronicheskoy progrediyentnoy
khoree (Huntington's chorea.) (Experience
in the use of neuroleptic substances in
chronic progressive chorea.) (Huntington's
chorea.) Journal of Neuropathology and
Psychiatry, 63(1):96-102, 1963.

During a 2-year period, 16 patients (5 men
and 11 women, 35 to 60 years of age)
suffering from Huntington's chorea were
treated with two neuroleptic preparations;
reserpine was administered to 10, and the
remaining 6 were treated with perphenazine.
All of the patients had been suffering from
the disease for over 5 years. Reserpine was
given in hourly doses of 3 to 4 mg and
perphenazine in doses of 36 to 60 mg.
Excellent results were achieved with both
preparations. Of nine patients who
received reserpine and completed the trial,
all improved significantly, and seven were
discharged from the hospital. Of six
patients treated with perphenazine, four
were discharged. The preparations proved
most effective in relation to choleretic
hyperkinesia. A notable reduction in the
frequency, rhythm, and amplitude of motor
and vocal activity was observed. The results
achieved with both neuroleptics are signifi-
cant, and perphenazine, in particular, is
recommended. No complications were noted
among patients who received perphenazine.
The recommended dosage of the drug at the
beginning of treatment is 12 mg, with slow
increases to a level of 36 to 60 mg.

Moscow, U.S.S.R.

2749 Marzollo, Marco. Il Ro 5-0690
(Librium) nella terapia di alcuni
stati di ipertiroidismo. (Ro 5-0690
(Librium) in the therapy of various
hyperthyroid states.) Minerva Medica,
54:1609-1614, 1963.

The use of chlordiazepoxide in the treatment
of hyperthyroidism is reported, based on
results with 39 patients, 8 males and 31

females, 16 to 75 years old. The patients were divided into four groups. Group 1, of 14 patients, was given chlordiazepoxide alone in doses of 20 to 40 mg daily. All patients showed a decrease in basal metabolism, and an increase in weight was noted in 60% of the cases. Group 2, of seven patients, was given chlordiazepoxide in combination with a synthetic antithyroid drug; two of these patients were also given I^{131} . Three patients, including the two treated with I^{131} , showed no change. The other four showed a decrease in basal metabolism and regression of tremor, fever, and subjective symptomatology. The dose of chlordiazepoxide was 20 to 50 mg daily; the antithyroid compounds were given in 50% to 70% of the usual dose. Group 3, of 15 patients, was given only antithyroid drugs. About 50% responded; best results were seen in younger patients and patients with a shorter duration of illness. Group 4, of three patients, was given a sedative (calcium bromide) i.v. Results were unsatisfactory in all cases. Certain early forms of hyperthyroidism and certain syndromes attributable to thyroid dysfunction may be treated without resorting to antithyroid drugs, which may be toxic.

La Memoria Public Hospital
Brescia, Italy

2750 Laura, L. & Vitetta, M. Il paraclorofenossiacetato di dietilaminoetanolo (ANP 235) in alcune sindromi neurologiche: Risultati clinici e considerazioni. (Diethylaminoethanol parachlorophenoxyacetate (ANP 235) in some neurological syndromes. Clinical results and discussion.) *Neuropsychiatria*, 18:319-333, 1963.

The use of diethylaminoethanol parachlorophenoxyacetate (ANP 235) in 46 patients, 20 females and 26 males, with various neurological syndromes is reported. The patient sample included 15 cases of meningoencephalitis, 10 cases of recent craniocerebral trauma, 10 cases of vascular ictus, 4 cases of epilepsy, and 3 cases of disturbed sleep-waking rhythm. The drug was given in doses of 500 to 1,000 mg/day for 5 to 60 days. Diagnosis, daily dosage, duration of treatment, therapeutic results, and side effects are listed for each of the 46 cases. The ANP 235 was found to possess the following four properties: (1) selective action that facilitated the reestablishment of consciousness; (2) normalization of the emotional-affective sphere; (3) normalization of psychomotor activity; and (4)

action on organic neurological symptoms. The drug was well tolerated and produced no untoward effects.

Queen Margaret Hospital
Messina, Italy

2751 Aleksandrowicz, Jerzy & Dzikowski, Henryk. Lucidril (ANP 235, centrophenoxine)—*Obserwacje nad działaniem leku. (Lucidril (A.N.P. 235, centrophenoxine)—Observations on the effect of the drug.)* *Neurologia, Neurochirurgia i Psychiatria Polska*, 13(1):97-101, 1963.

Fifty-one neurotic and psychotic clinical patients of both sexes were treated in groups of varying sizes and according to their symptoms with centrophenoxine. Six clinic workers who acted as controls received one 0.1-mg tablet of centrophenoxine. Three of the controls developed side effects that are similar to those observed with amphetamine—overstimulation and lightheadedness, followed by tiredness and drowsiness. The other three controls had significant effects. Of the 15 patients who were comatose, 13 showed marked improvement after treatment with centrophenoxine from 4 to 9 days. Dosages were 250 mg i.v. or i.m. or 200 mg in simply syrup. One patient, who had been in a continuous coma, developed inflamed lungs and convulsions, and died. One patient was not aided by the drug. Of 10 psychotics treated over 13 days, 6 schizophrenics showed only temporary relief, immediately after the drug was administered, and there was improvement in four patients of this group who were treated for catatonic stupor. Of six depressives and three schizophrenic delusives, one case showed some improvement, seven showed no change, and one worsened. Of 10 neurotics, 4 showed slight improvement, 4 no change, and 2 worsened. In the eight cases of dullness, two worsened, and the other six did not show recognizable signs of improvement. In these last three groups, the drug was initially administered in doses of 300 t.i.d.; later the dose was increased to 600 mg/day, and 10 patients received up to 1,000 mg/day for a few days. The courses of treatment varied from a few days to 35 days with a 13-day average. Side effects were noted in five cases. The most common were irritability and restlessness. In three cases, the drug had to be discontinued, and in two cases, the side effects were relieved with meprobamate. Three other cases exhibited excessive drowsiness. These side

Effects were most commonly observed among neurotics and those suffering from dementia. Due to its action, centrophenoxine cannot be considered a neuroleptic nor an antidepressive.

Psychiatric Clinic of the
Academy of Medicine
Warsaw, Poland

2752 Sasaki, Iwane, Hara, Toshio, Asagami, Yoshifum, Yamada, Michio, & Fukunaga, Higezo. (Clinical effect of thioridazine Melleril.) Journal of the Yamaguchi Medical Association, 12(2):154-162, 1963.

Thioridazine was administered to patients, mainly schizophrenics, with chronic symptoms and to some neuroasthenic children. The initial dose of thioridazine was 100 mg/day, gradually increasing for the schizophrenics. Maximum dose was 800 mg/day (average dose, 200 to 400 mg/day as maintenance dose). In the neuroasthenic children, the average dose was 10 to 25 mg/day. The following results were observed: In schizophrenic patients, 27 (64%) cases out of 42 showed symptomatic improvement. In 25 cases of patients with chronic illnesses lasting more than 3 years, 15 cases (60%) showed symptomatic improvement; in 13 cases of schizophrenic patients with illnesses of less than 3 years, 11 cases (84%) showed improvement. The specific sedative effect of thioridazine was observed in all cases. Behavioral disorders were corrected and learning ability was enhanced in neuroasthenic patients. Side effects, such as those seen with chlorpromazine, were very rarely observed.

Department of Neuropsychiatry
Yamaguchi Medical School
Yamaguchi, Japan

2753 Yamauchi, I. (Studies on the effects of fluphenazine upon minor tremor (MT) and EEG in schizophrenics by automatic frequency analyzer.) Brain and Nerve, 15(7):641-650, 1963.

The frequency-distribution patterns of minor tremor, EEG's and extrapyramidal symptoms were analyzed in relation to the therapeutic effects of fluphenazine in the treatment of 17 schizophrenic patients. The minor tremor (MT) and EEG were studied prior to, and at

intervals during, drug therapy. Fluphenazine was administered in doses of 1 mg/day, gradually increasing to 3 mg/day; after the 15th day, the doses were adjusted individually. There was slight improvement in those cases with typical frequency distribution of MT before medication, regardless of the alteration of the distribution pattern by medication. In cases with atypical frequency distribution of MT before medication, in which the MT showed a typical pattern following medication, there was improvement; in those cases in which MT remained unchanged, there was no improvement. The extrapyramidal symptoms were less frequent in those patients having a typical MT pattern during medication. In nine patients, there was no parallel relationship between the MT and EEG frequency distribution. The EEG frequency-distribution pattern was not related to therapeutic effects of extrapyramidal symptoms.

Department of Neuropsychiatry
Kurume University
School of Medicine
Kurume, Japan

2754 Koutsky, Carl D. & Sletten, Ivan W. Chlordiazepoxide in alcohol withdrawal. Minnesota Medicine, 46:354-357, 1963.

A double-blind study was conducted to test the efficacy of chlordiazepoxide in 11 chronic alcoholics suffering from acute withdrawal symptoms. The age range of the patients was from 38 to 58 years (average, 50.7 years), and the average estimated duration of suffering was 14.6 years. Each patient received a total of 300 mg i.m. of either chlordiazepoxide or placebo in three injections every 8 hours for the first 24 hours. Nine of the patients also received paraldehyde p.o. The patients remained in the hospital for an average of 13 days. After the first and second 24-hour periods, the professional staff rated the patient as drug treated or placebo treated. Out of a possible 27 guesses by the staff, there were 12 correct and 10 incorrect guesses. The only side effect observed was one case of mild ataxia. This study indicates that i.m. administration of chlordiazepoxide has little influence on the alcohol withdrawal syndrome.

Adult Psychiatric Inpatient Service
University of Minnesota Hospitals
Minneapolis, Minnesota

2755 Millan, Jorge & Martinez, Roque.
**Accion de la flufenazina en
 pacientes con lesiones dermatologicas
 asociadas a tension y ansiedad. (Action of
 fluphenazine on patients with dermatological
 lesions associated with tension and anxiety.)**
 Prensa Medica Mexicana, 28:96-97, 1963.

Fluphenazine chlorhydrate was tested in 31 patients with various dermatological lesions associated with tension and anxiety. The drug was given in doses of 1 to 2 mg every 12 to 24 hours. Average duration of treatment was 3 months. Results were good in 29 patients and poor in 2. The drug was discontinued in only one case. Side effects were minimal and reversible.

Dermatological Department
 Clinic No. 5
 Mexico City, Mexico

in the lower extremities were noted. Parkazin is indicated in all cases of parkinsonism because of its antitremor action.

Nervous and Mental Division
 Gyula County Hospital
 Gyula County, Hungary

See also: 2675, 2680, 2683, 2694, 2696, 2704, 2786, 2787, 2808, 2812, 2817, 2824

2756 Dobi, Sándor. Tapasztalataink
 Parkazinnal, és annak egyéb anti-
 parkinsonos gyógyszerrel való kombináció-
 jával. (Our experience with Parkazin and
 its other combinations with antiparkinsonian
 drugs.) Ideggyógyászati Szemle, 16:232-237,
 1963.

The antiparkinsonian drug Parkazin (N-2-diethylaminoethylphenothiazine HCl) was tested in 31 patients, 21 males and 10 females, 28 to 70 years of age, with parkinsonism or paralysis agitans. Duration of treatment was 3 to 9 weeks on an in-patient basis; some patients were continued on the drug as outpatients. Treatment was initiated with 250 mg Parkazin i.m. or 125 mg i.v. daily for about 4 days. If larger doses were needed, additional drug was given p.o. A dose of 450 to 500 mg daily was usually satisfactory; no patient received more than 750 mg daily. Improvement was usually noted 4 to 5 days after the start of treatment. The drug produced a profound muscle-relaxing effect in all patients. Of the 31 patients, 28 showed a reduction in intensity and amplitude of tremor; in three patients, the drug had no antitremor effect. Best results were achieved in patients with a duration of illness of not more than 2 to 3 years. Since Parkazin had little effect on vegetative phenomena, it was combined with drugs containing belladonna alkaloids, such as Bellafit. Side effects occurred in 25% of the patients; drowsiness, weakness, and pain

SIDE EFFECTS

757 Jacobziner, Harold & Raybin, Harry W.
Phosphorus, trifluoperazine, and
methyl alcohol intoxications. New York
State Journal of Medicine, 63:2705-2707,
1963.

Seven cases of poisoning reported to the New
York City Poison Control Center are described.
Case 1, a 38-year-old woman ingested
each paste containing phosphorus. Cases
through 4 were siblings, a boy (5 years
age) and two girls (3½ years and 10
months of age, respectively) who were treated
for trifluoperazine poisoning. Case 5 was
a dog poisoned with Lindane, a topical man-
gling. This drug is also used to treat
scabies in human patients. Case 6, a 53-
year-old male, died of methyl alcohol poison-
ing. In Case 7, a 2½-year-old boy ingested
tablets containing 3.33 mg methamphetamine
1 and 21.6 mg phenobarbital. The pheno-
barbital component in this medication was
not sufficient to control the amphetamine-
induced increase in motor activity.

Poison Control Center
New York City of New York
Department of Health
New York, New York

758 Okubo, Hiroshi. (Blood reactions to
drugs.) Acta Haematologica, 26:267-
275, 1963.

The problems of drug-induced dyscrasias and
their diagnosis and therapy were discussed.
The drugs that often cause granulocytopenia
are sulfonamides, analgetics, antipyretics,
and sedatives, whereas chloramphenicol,
sphenamine, and thiacetazone tend to in-
duce pancytopenia. Thrombocytopenia is often
caused by sulfonamides, chloramphenicol,
chlorothiazide, and quinidine. Hemolytic
anemia or erythroid hypoplasia without
pancytopenia have also been found to be types
of drug-induced blood dyscrasias. The most
reliable method to determine the responsible
drug seems to be the provocation test. In
out of 11 cases with granulocytopenia in
which this method was used, a decrease of

30% in the neutrophil count occurred after
provocation. Early detection and prompt
withdrawal of the suspected drugs are the
first steps of treatment. Hormones (adreno-
cortical steroids and ACTH) have been found
to be effective in 30% of granulocytopenia
cases.

Kansai Medical School
Moriguchi, Osaka, Japan

2759 Gerber, E. L. Sluchay nekroti-
cheskogo nefroza pri aminazinoterapii.
(Necrotizing nephrosis in a patient treated
with chlorpromazine.) Zhurnal Nevropato-
logii i Psikiatrii imeni S.S. Korsakova,
63(8):1217-1222, 1963.

A case history is presented of a 67-year-old
schizophrenic woman with hypertonia, who
developed nephrosis with uremia after chlor-
promazine treatment. The patient had
suffered from hypertonia for 14 years.
During prior treatment, the patient had
received chlorpromazine 200 mg/day for 2
months. Upon hospital admission, the
patient was given chlorpromazine 50 mg/day
for 6 days. On the seventh day, the patient
developed a high temperature, which was
treated with penicillin and streptomycin.
Thirteen days after the intake of chlor-
promazine, the patient's residual nitrogen
content in the blood rose from 50 to 476
mg percent, and the urea content in the
blood rose from 60 to 520 mg percent. The
patient died on the 15th day. Great pre-
cautions must be observed during the adminis-
tration of chlorpromazine to elderly
patients with hypertonia; special attention
should be given to arterial pressure and
kidney function.

The Patho-Morphological Laboratory of the
Psychiatric Institute
Academy of Medical Sciences
Moscow, U.S.S.R.

2760 Boháček, N., Hajnšek, F., & Sartorius, N. **Extrapyramidale Symptome bei der Anwendung von Psychopharmaka.** (Extrapyramidal symptoms in treatment with psychotropic drugs.) Fortschritte der Neurologie, Psychiatrie und Ihrer Grenzgebiete, 31(30): 565-570, 1963.

A graph of 17 phenothiazines is given, which shows the transition of drugs from one extreme, consisting of sedative action, vegetative side effects, and other effects, to the other extreme, consisting of a predominance of cataleptic action and extrapyramidal side effects. The graph also indicates average therapeutic doses and relative efficacy of the drugs. Deviations from the general classification, which are due to sex and age, are described in detail. The following generalizations may be made: (1) the appearance of the extrapyramidal syndrome is not essential in order to obtain a therapeutic effect. (2) The more effective drugs usually do produce the extrapyramidal syndrome. (3) Somatic and psychological individual predispositions influence the appearance of the syndrome. (4) The duration of illness appears to be unrelated to the occurrence of a drug-induced extrapyramidal syndrome. (5) More akinetic--hypertonic than hyperkinetic--dystonic syndrome types are observed with phenothiazines. (6) The order of appearance of syndrome types during a course of medication is dyskinesia, akathisia, and parkinsonism. (7) The extrapyramidal syndrome can usually be controlled by reducing the dosage or by the simultaneous administration of antiparkinsonian drugs.

Neurological-Psychiatric Clinic
University of Zagreb
Zagreb, Yugoslavia

2761 Zetler, G. **Die antikataleptische Wirksamkeit einiger Antidepressiva (Thymoleptica).** (The anticataleptic activity of several antidepressant drugs (thymoleptics).) Arzneimittel-Forschung, 13(2):103-109, 1963.

The anticataleptic activity of various antidepressants was tested in male mice (23 to 27 g in weight) with the cataleptic state induced by s.c. injection of bulbo-carpine, chlorpromazine, prochlorperazine, chlorprothixene, or perphenazine. The antidepressants tested included amitriptyline, imipramine, several imipramine derivatives, iproniazid, isocarboxazid, and

ethyltryptamine. Amphetamine was used as the anticataleptic standard. Amitriptyline showed greater anticataleptic activity than imipramine. There was wide variation in the anticataleptic activity of MAO inhibitors, indicating that inhibition of brain monoamine oxidase is not the source of anticataleptic activity. The activity exhibited by the antidepressants was easily distinguished from that of amphetamine. It is suggested that this test for anticataleptic activity in mice is an effective screening method for possible antidepressants.

University of Kiel
Kiel, Germany

See also: 2681

BEHAVIORAL STUDIES

62 Smythies, J. R. The mode of action of mescaline. In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. Hallucinogenic drugs and their psychotherapeutic use. Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. First session, p. 17-30.

Experiments in rabbits with mescaline, performed for the purpose of eliciting the mode of action of mescaline, have shown that large doses of mescaline cause an initial inhibition of the responses and an increase in latency, followed by a facilitation and decreased latency. The inhibitory effect may fall on multisynaptic pathways, but it may preferentially affect the pathways responsible for the later responses (facilitation and decreased latency). No speculation is made as to the site or mode of action of mescaline, because of the unknown physiological mechanisms responsible for the late responses.

Department of Psychological Medicine
University of Edinburgh
Edinburgh, Scotland

63 Bradley, P. B. & Key, B. J. Conditioning experiments with LSD. In: Crocket, Richard, Sandison, R. A., & Walk, Alexander, eds. Hallucinogenic drugs and their psychotherapeutic use. Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. First session, p. 4-11.

The results of both electrophysiological and conditioning experiments in cats given LSD ($\mu\text{g}/\text{kg}$ to $1 \text{ mg}/\text{kg}$) are reported and discussed. It appears that LSD has a site of action closely related to the neurophysiological mechanisms concerned with the filtering and integration of sensory information. The action of LSD seems to be selectively related to sensory influences on the diffuse systems of the brain and, especially, on the arousal system at the brain-stem level. The distortions of sensory

perception that occur in drug-induced hallucinatory states might be explained by such a mechanism of action.

Department of Experimental Neuropharmacology
University of Birmingham
Birmingham, England

2764 Saakyan, S. A. K voprosu o vliyani aminazina na uslovnoreflektornuyu deyatel'nost'sobak. (On the influence of Aminazine on conditioned-reflex activity of dogs.) Zhurnal Eksperimental'noi i Klinicheskoi Meditsiny, 3(2):11-16, 1963.

In contrast to other studies that investigated the action of chlorpromazine on developed conditioned reflexes, this study investigated the acquisition of conditioned reflexes in dogs that had been given chlorpromazine. Light from a light generator stimulator, with a frequency of 10 seconds, an intensity of 0.6 joule, and with a bell, was used as conditioning stimulus. The unconditioned stimulus was an electric current with a frequency of 20 cycles and a continuing impulse of 1/4 second applied to the right front paw. The stimulants were usually applied from 8 to 12 times, with the conditioned stimulant lasting 5 seconds and the unconditioned stimulus lasting from 0.5 to 1 second. It was found that chlorpromazine produced a two-phase reaction. The first phase was characterized by the general excitation of the animal and activation of the EEG. The second phase was characterized by the development of a specific deactivating effect of chlorpromazine. Chlorpromazine in doses from 1.5 to 5 mg/kg completely excluded the formation of conditioned defensive reflexes. One mg/kg of chlorpromazine appears to be the threshold dosage under which formation of conditioned reflexes can occur.

L. A. Orbeli Physiological Institute
Armenian Academy of Sciences
U.S.S.R.

2765 Vasilevskaya, N. Ye. *O roli retikul-yarnoy formatsii i perednikh poley limbicheskoy kory v elektrokortikograficheskom otobrazhenii khimicheskikh izmeneniy vo vnutrenney srede.* (On the role of the reticular formation and anterior poles of the limbic cortex in the electrocorticographic picture of chemical changes in internal environment.) *Fiziologicheskii Zhurnal SSSR imeni I. M. Sechenova*, 49:293-298, 1963.

An experiment was conducted to investigate changes in the rabbit's electrocorticogram as a result of an administration of either HCl i.p. or NaCl i.v. following i.v. administration of chlorpromazine or extirpation of the limbic region of the cortex. Twenty rabbits were used in the experiments. The stimulants were either an i.p. infusion of a 0.5% solution of 100 ml HCl or an i.v. infusion of a 5% solution of 10 ml NaCl. Eleven rabbits received chlorpromazine i.m. in doses from 1 to 5 mg/kg of body weight. In five rabbits, bilateral extirpation of the anterior limbic region was performed, and four rabbits received a controlled unilateral extirpation of the limbic region. The operations were performed 5 to 7 days prior to the experiment. Chlorpromazine (3 and 5 mg/kg) eliminated the changes in the electrical activity, produced by the 0.5% solution of HCl and by the 5% solution of NaCl, of the motor and parietal regions of the cerebral cortex. The bilateral extirpation of the limbic region of the cortex also eliminated the electrical activity of the motor and parietal regions produced by the introduction of a 5% solution of NaCl. The unilateral extirpation of the limbic region did not eliminate the electrical action produced by the introduction of a 5% solution of NaCl.

The Physiology Division
Leningrad University
Leningrad, U.S.S.R.

2766 Yakovleva, Ye. A. *K mekhanizmu vliyaniya aminazina na tsentral'nuyu nervnuyu sistemu.* (On the mechanism of action of Aminazine on the central nervous system.) *Zhurnal Vysshei Nervnoi Deiatel'-nosti imeni I.P. Pavlova*, 13(2):267-275, 1963.

The action of chlorpromazine was investigated on the CNS of dogs, rats, and frogs. The rats were injected i.m. with a 2.5% solution of chlorpromazine at a dose of 3 mg/kg. The frogs received i.m. doses

ranging from 10 mg to 25 mg/kg. The neurotic dogs who refused to eat in a conditioned reflex chamber were injected with 0.5 mg/kg of chlorpromazine. Chlorpromazine inhibited the respiratory function and motor activity in dogs, rats, and frogs; this action was achieved after an intake of small doses in dogs, and after large doses of 25 mg/kg in frogs. Chlorpromazine inhibited the food, acid, and electrodefensive conditioned reflexes in dogs. The drug potentiated the activity of the food unconditioned reflex in rats and dogs as manifested when the animals showed increased excitability when presented food and when increased conditioned salivation occurred. Chlorpromazine has a twofold action on nervous system formations—it either changes the composition and properties of the medium surrounding the nerve cells (its effect is momentary), or it changes the histochemical structure of the nervous tissues (its effect is prolonged).

Institute of Normal and
Pathological Physiology
U.S.S.R. Academy of Medical Sciences
Moscow, U.S.S.R.

2767 Grandjean, E. *Die Wirkung von Trichloräthylen auf das Verhalten von Ratten.* (The effect of trichloroethylene on rat behavior.) *Pharmaceutica Acta Helvetiae*, 38:464-469, 1963.

The effect of trichloroethylene vapor was studied on the swimming performance and on the motor activity of rats. Swimming performance was measured after a 6-hour exposure to the vapor by the method of Batting, and motor activity was measured during a 5-hour exposure using cages, constructed for automatic recording of activity, set up in the vapor chamber. In the swim tests, 6 test and 6 control rats were exposed to concentrations of 400 and 800 ppm. Rats were given a supplementary load (a 27-g weight fixed to the tail) to test the effect of additional stress on swimming. At 400 ppm, only rats with a supplementary load were slowed; at 800 ppm all rats swam slower. One hour after exposure, swimming time returned to normal. In the motor activity tests, 12 test and 12 control animals were exposed to 400, 800, or 1,600 ppm trichloroethylene. The motor activity of rats was reduced both 20 and 80 minutes after exposure. The average

duction in activity was statistically significant only at concentrations of at least 1,600 ppm trichlorethylene.

Institute for Hygiene and Labor Physiology
Federal Technical University
Zürich, Switzerland

68 Pickenhain, L. Die Anwendung einer experimentellen Trinkneurose bei Ratten zur Differenzierung zentral wirksamer Pharmaka. (The use of an experimental drinking neurosis in rats for the differentiation of drugs with central action.) *Zeitschrift für Allgemeine Biologie und Medizin*, 10:549-553, 1963.

The differentiating action of methylpentynol (10 and 80 mg/kg), chlorpromazine (1 mg/kg), and benactyzine (1 mg/kg) on shock-induced neurosis in 6-month-old rats (250 to 300 g body weight) was investigated. Neurosis was produced by the application of electrical shocks to rats while they attempted to drink following the ingestion of food. The subjects were tested prior to and following injections of the drug or physiological saline. Drugs were administered on a blind basis. Methylpentynol produced an increase in drinking attempts at both dosages when contrasted with the controls, despite the shock. The feeding periods were not affected. Repetition of drinking attempts in methylpentynol-treated rats did not occur even when the voltage was increased to 30 volts. Benactyzine had no effect on drinking attempts, and chlorpromazine produced a decrease in drinking attempts.

Pharmacological Institute
Medical Academy
Münster, Germany

69 Cohen, Sidney & Edwards, Allan E. The interaction of LSD and sensory deprivation: Physiological considerations. *Recent Advances in Biological Psychiatry*, 1:139-144, 1963.

The physiological interaction of LSD and sensory deprivation was studied in 10 healthy, volunteer subjects. They were studied at weekly intervals according to four conditions in random sequence: (1) LSD, 50 µg p.o., plus sensory normalcy (SN); (2) LSD, 125 µg p.o., plus sensory deprivation (SD); (3) identical placebo, plus SN;

and (4) identical placebo, plus SD. The following physiological measurements were made during the 2-hour period: heart rate, EKG, respiration rate, finger pulse volume (plethysmograph), skin resistance, and EEG. Those subjects who had received LSD without SD were able to identify what they had been given. Six of the 10 who received LSD plus SD answered "nothing" or "placebo." The heart rate and the skin resistance of the subjects under the LSD-SN condition were significantly increased. The vasoconstriction under both LSD conditions was significantly different from that under the placebo conditions. The percentage of time in which the EEG frequency was greater than 14 cycles/second depended upon which sensory state the subject was in, but the LSD-SD subjects were different from the placebo-SD subjects. There was no significant difference in the respiration rate following LSD. The placebo-SD subjects had the most inactive pattern during the last half of the 2-hour session. The highest activation was obtained by the LSD-SN subjects.

(No address)

2770 Lancier, J., Plas, R., & Naquet, R. Étude neurophysiologique comparée de trois drogues psychotropes. (Comparative neurophysiological study of three psychotropic drugs.) *Journal de Physiologie*, 55(2):281-282, 1963.

The neurophysiological effects of chlor-diazepoxide, amitriptyline, and dibenzoazepinyl piperazine were compared in acute waking cat preparations. The effects of the compounds were determined on cortical rhythm, on the hippocampal threshold of arousal produced by reticular stimulation, and on potentials evoked at the level of the mesencephalic reticulum. The duration of postdischarge induced by amygdaloid stimulation before and after each fractional injection was also studied. The action of dibenzoazepinyl piperazine approximated that of the thymoleptic imipramine. The action of chlor-diazepoxide was identical to that of the tranquilizer meprobamate. Amitriptyline possessed the action of chlorpromazine on cortical rhythms and the threshold of arousal through reticular stimulation and the action of imipramine on the hippocampus. The drugs possess both neuroleptic and thymoleptic action. All these drugs inhibited the postdischarge.

Laboratory of Pharmacology
Medical School
Nancy, France

2771 Schneider, J., Thomalske, G., Trautmann, P., Smolarz, R., & Sabbagh, R. *Le comportement EEG de l'homme et de l'animal soumis à l'action progressive du 4-hydroxybutyrate de sodium.* (The EEG behavior of humans and animals subjected to the progressive action of sodium 4-hydroxybutyrate.) *Agressologie*, 4:55-70, 1963.

Alterations in EEG activity produced by sodium- γ -hydroxybutyrate were studied in cats, rabbits, and humans. The EEG's were recorded at dose levels of 70 to 350 mg/kg, 350 to 1,250 mg/kg, 1,000 to 1,800 mg/kg, 2,000 to 2,500 mg/kg, and over 2,500 mg/kg. The drug was administered slowly by infusion or rapidly by injection. Both the rabbit and cat were resistant to the drug, showing anesthetic drowsiness only at excessive doses. In man, contrary to classic anesthetics, sodium- γ -hydroxybutyrate produces no rapid, barbiturate-type EEG phase whether injected in massive doses or infused slowly. Initial delta activity is accompanied by slight drowsiness; the anesthetic phase is characterized by muscular relaxation and electrical silence. The EEG observations in animal and human subjects for each dosage level are described. The electrical silence observed in the human anesthetic phase is discussed.

Pasteur Hospital
Colmar, France

2772 Hausner, M. & Dolezal, V.
Catamnesic evaluation of psychotherapeutic results with the use of LSD. *Activitas Nervosa Superior*, 5(2):215-216, 1963.

The results of a followup study of four groups of patients who participated in an LSD study 1 year previously are reported. In the previous study, LSD had been evaluated as an adjunct to psychotherapy in the treatment of neuroses. The patients had been treated as follows: (1) control group, no injection; (2) patients given 100 μ g LSD in individual sessions; (3) patients given 50 μ g LSD in group sessions; and (4) patients given physiological saline rather than LSD. All patients were given the same type of psychotherapy. The condition of the patients 1 year after treatment was assessed by a variety of standard questionnaires. Results showed that the use of LSD in the psychotherapeutic process is justified. The use of LSD without psychotherapy is not advised.

(No address)

2773 Molinengo, L. *Profilo psicofarmacologico del meprobamato.* (Psychological profile of meprobamate.) *Archivio Italiano di Scienze Farmacologiche*, 12:118-129, 1962.

The effects of meprobamate on behavior in rats were studied in three experimental situations: concurrent variable-ratio avoidance, guided extinction, and simple extinction. Thirty albino rats, 15 males (250 to 300 g in weight) and 15 females (200 to 250 g in weight), were divided into three groups of 5 males and 5 females each. Meprobamate dosages were as follows: (1) concurrent variable-ratio avoidance—0.08, 0.16, 0.25, and 0.32 g/kg; (2) guided extinction—0.004 and 0.16 g/kg; and (3) simple extinction—0.04 and 0.16 g/kg. Meprobamate reduced food motivation more in females than in males. Reduction in environmental conditioning was evident in males only. Meprobamate reduced right-left discrimination to the same extent in both sexes. Shock motivation was modified at the highest doses. In certain cases, irreversible modifications of behavior were observed in guided extinction and simple extinction tests.

University of Torino
Torino, Italy

2774 Babbini, M., Montanaro, N., & Casoli, R. *Analisi di alcune variabili che influenzano la motilità del ratto albino in condizioni di controllo e di trattamento farmacologico.* (Analysis of some variables that influence motility of the albino rat in control conditions and under pharmacological treatment.) *Archivio Italiano di Scienze Farmacologiche*, 13:141-143, 1963.

The periodicity of motility, an experimental variable, was studied in 48 Wistar and 48 Sprague-Dawley male, albino rats (300 to 350 g in weight). The animals were given 20 mg/kg of caffeine i.p. before measuring the motility by means of an actograph. The controls received physiological saline. The experimental design consisted of four factors using 16 combinations of two each: time of day (two periods, midnight to 7 a.m. and 10 a.m. to 5 p.m.); two strains of rats; conditioning to light and dark; and pharmacological treatment under conditions of light and dark. The motility of both strains was less during the day than at night and was less in illumination than in darkness. In comparing the interaction of night and day versus the control and

drug-treated groups, the results showed that the influence of the time of day on motility was not additive to the pharmacological effect, but rather that the two effects potentiated each other. In the studies on the comparison of the interaction of night and day versus light and darkness, a 24-hour activity rhythm in the albino rat was observed, and this rhythm was potentiated in a multiplicative manner by the factor of illumination. The motility of the Wistar rats was less than that of the Sprague--Dawley strain.

Institute of Pharmacology
University of Bologna
Bologna, Italy

2775 Nedoma, K. **Psychotherapy of sexual neuroses.** Ceskoslovenska Psychiatrie, 9(1):28-32, 1963.

Psychotherapeutic techniques used in the treatment of sexual neuroses are described. An example of this treatment is reported in a 31-year-old man. The patient was treated at the beginning of psychotherapy with sedatives, which relieved his irritation, but did not change the sexual disturbance.

Institute of Sexology
Faculty of General Medicine
Prague, Czechoslovakia

2776 Baccelli, G., Guazzi, M., Libretti, A., & Zanchetti, A. **Effects of pressor- and chemoceptive components of the cat's aortic nerve on sham rage behaviour.** Experientia, 19:1-6, 1963.

Electrical stimulation of the left aortic nerve of 14 acute thalamic cats was performed in order to determine the pressor- and chemoceptive effects on sham rage behavior. Arterial pressure and respiration were measured. The threshold effects of low-voltage, short pulse aortic stimulation, with a background of quiet behavior, were slight hypotension, transient decrease of respiratory movements, and no overt change in behavior. A moderate increase in either pulse amplitude or duration (e.g., from 1 to 2 to 3 V or from 0.01 to 0.02 to 0.03 msec) induced marked hyperpnea in the cats culminating in a pattern rage reaction with an increase in hyperpnea, blood pressure rise, mydriasis, and struggling movements. Further increase

did not change the type of response. Threshold stimuli, during recurring outbursts of rage, blocked all somatic and autonomic manifestations of the spontaneous rage fits. Slight increase in either amplitude or duration of the stimulating pulses changed the inhibitory effect into an excitatory effect, with the recurring rage behavior being markedly intensified.

Institute of Medical Pathology
University of Siena
Siena, Italy

2777 University of Pisa. **Neurophysiological studies of conditioning.** Technical report, Ricci, Gianfranco, Pisa, Italy, 1 May, 1963, 13 p. Grant AF-EOAR 62-102, unclassified report.

The modifications of the acquisition and performance of the avoidance conditioned responses have been studied in the monkey during administration of atropine, eserine, and amphetamine. The modifications of the pupillary amplitude during conditioning to a sound and their correlations with modifications of amplitude of the evoked cortical responses to a flash were also studied. In the first experiment, four *Macacus rhesus* monkeys were conditioned to avoid a painful shock (UCS) upon presentation of a short-lasting light (DS) or a sound (CS). Atropine (0.5 mg/kg s.c.) in doses with little or no effect on EEG arousal, impaired the acquisition of CR in the control monkeys and caused a decreased generalization of the responses to the negative stimulus in well-trained animals. In doses sufficient to block the EEG arousal, atropine (0.8 to 1.25 mg/kg s.c.) also caused a disappearance of the CR. Both EEG arousal and the CR's could be found in the monkey only when amphetamine (2 to 3 mg/kg) was given to monkeys previously treated with atropine (3 to 5 mg/kg). In the second experiment, pictures were taken of the monkey's eyes during one single flash of light that was elicited at various intervals from the onset of the CS. The cortical responses evoked by the flash were simultaneously recorded on the oscilloscope. A slight pupillary constriction during the first part of the conditioned trial was followed by a slight pupillary dilatation that occurred during the CR. The facilitation of the visual cortical responses observed during conditioning was found to occur during both the pupillary constriction and the first part of pupillary dilatation.

BEHAVIORAL STUDIES

The modifications of the cortical responses to flashes are, therefore, not related to changes of amplitude of the pupils.

Department of Pharmacology
University of Pisa
Pisa, Italy

See also: 2684, 2706, 2734, 2735, 2779,
2825, 2829

PHARMACOLOGY

2778 Bush, Milton T. C. **Sedatives and hypnotics. 1. Absorption, fate, and excretion.** In: Root, Walter S. & Hofmann, Frederick G., eds. *Physiological pharmacology. A comprehensive treatise. Volume I. The nervous system—Part A. Central nervous system drugs.* New York, Academic Press, 1963, p. 185-218.

These agents classified as sedatives, hypnotics, and anesthetics that produce simple general depression of the CNS are discussed in terms of their pharmacological parameters, solubility, ionization, absorption, distribution, metabolism, and excretion. The general relationships of solubility and ionization to absorption, distribution, metabolism, and excretion for the hypnotics and the hypnotic-anesthetics are presented, after which the parameters are summarized for the barbiturates as a group. For the parameters of the nonbarbiturates, each of the following compounds are presented individually: chloral hydrate, paraldehyde, methyprylon, ethinamate, glutethimide, bromide (as sodium bromide), and magnesium (as magnesium sulfate). (101 references)

Department of Pharmacology
Vanderbilt University School of Medicine
Nashville, Tennessee

2779 Lewis, J. J. **2. Rauwolfia derivatives.** In: Root, Walter S. & Hofmann, Frederick G., eds. *Physiological pharmacology. A comprehensive treatise. Volume I. The nervous system—Part A. Central nervous system drugs.* New York, Academic Press, 1963, p. 479-523.

The action of the Rauwolfia derivative, reserpine, and other similar compounds on the CNS is discussed. The chemistry, pharmacology, clinical use, and side effects of reserpine are presented. The nature of the actions of reserpine on the nervous and cardiovascular systems remains unclear due to the contradictory work performed at the biochemical, neurophysiological, and electrophysiological levels. Reserpine, however,

does alter the brain levels of the catecholamines, serotonin, and GABA. It also alters the electrical activity of parts of the brain.

Institute of Physiology
Glasgow University
Glasgow, Scotland

2780 Brazier, Mary A. B. **2. Effects upon physiological systems. a. The electrophysiological effects of barbiturates on the brain.** In: Root, Walter S. & Hofmann, Frederick G., eds. *Physiological pharmacology. A comprehensive treatise. Volume I. The nervous system—Part A. Central nervous system drugs.* New York, Academic Press, 1963, p. 219-235.

The electrophysiological effects of sub-anesthetic doses and of anesthetic doses of barbiturates in man and in animals are discussed. Special attention is given to the effects of the barbiturates in animals in regard to the cortical receipt of sensory impulses and the routes taken within the brain by impulses from the sensory organs.

Brain Research Institute
University of California
Los Angeles, California

2781 Sherrod, Theodore R. **3. Diphenylmethane derivatives.** In: Root, Walter S. & Hofmann, Frederick G., eds. *Physiological pharmacology. A comprehensive treatise. Volume I. The nervous system—Part A. Central nervous system drugs.* New York, Academic Press, 1963, p. 537-561.

The action of the following four diphenylmethane derivatives on the CNS is discussed: hydroxyzine, benactyzine, azacyclonol, and pipradrol. The following information is given for each of these drugs: chemistry, pharmacology, therapeutic applications, toxicity, and clinical side effects. These

drugs are most frequently employed as depressants in mild emotional or mental disturbances, which are characterized by anxiety, tension, and agitation.

University of Illinois
College of Medicine
Chicago, Illinois

2782 Université Laval. Neurohumoral control of thyrotropic activity.

Final report, Fortier, Claude, Quebec, Canada, 1 October, 1960-31 May, 1963, 50 p. Grant AF-AFOSR 61-15, unclassified report.

The final report on studies concerning the neurohumoral control of thyrotropic activity is presented. Changes in ACTH and TSH secretion, induced by stress, thyroidectomy, adrenalectomy, or thyroid hormone administration, were determined in terms of altered rates of synthesis, release, or disappearance by measuring, as a function of time following a stimulus, their concentrations in the pituitary and blood and by measuring their rates of disappearance following exogenous administration. Inferred changes in the synthesis, release, or inactivation of the trophic hormones were correlated with the concentration of their respective target hormones in the blood. Improved bioassay techniques for determining ACTH and TSH and the programming for the IBM-1410 computer are described. Manuscripts reporting studies on the role of the hypothalamus in the maintenance of basal adrenocorticotrophic activity and on the site of the steroid--ACTH feedback are appended.

Faculty of Medicine
Laval University
Quebec, Canada

2783 Civil Aeromedical Research Institute.

Effects of some tranquilizing, analeptic and vasodilating drugs on physical work capacity and orthostatic tolerance. Ganslen, R. V., Balke, B., Nagle, F. J., & Phillips, E. E., Oklahoma City, Oklahoma, December 1963, 8 p. Grant 6364, unclassified report.

The effects of one tranquilizing and two analeptic agents on physical work capacity and on cardiovascular responses to postural changes were determined in five healthy

male subjects, aged 29 to 54 years. Two testing procedures were used: a tilt-table test for the assessment of orthostatic tolerance, and a treadmill test for the determination of aerobic work capacity and of the quality of functional adjustments. The following drugs and dosages were used: (1) caffeine and pentylenetetrazol separately and combined in a tablet containing 0.2 g caffeine and 0.4 g pentylenetetrazol; (2) Recordil (flavon-7-ethyl oxyacetate), given in a single 200-mg dose; and (3) meprobamate given in a clinical dose of 400 mg five times daily and in single doses of varying amounts. A definite increase in work capacity was observed after ingestion of a combined caffeine--pentylenetetrazol preparation, apparently resulting from an increased capacity for cardiac output and maximum oxygen intake. Recordil also improved work capacity but caused a tendency for orthostatic syncope, probably due to its general vasodilating effects. Meprobamate produced blood-pressure depression in doses over 1,200 mg/day. No syncope was observed. The drop in blood pressure creates a serious problem in sedated subjects operating aircraft or motor vehicles. Serious incident may be precipitated by emotional indifference to emergencies or as a consequence of delayed circulatory responses during flight maneuvers.

Civil Aeromedical Research Institute
Oklahoma City, Oklahoma

2784 University of Milan. Action of curare-like drugs on short and long neuronal circuits. Spinelli, D., Gualtierotti, T., Passerini, D., & Margari R., Milan, Italy, 1963, 1 p. Contract AF 61 (052)-23, unclassified report.

The effects of α -tubocurarine and succinylcholine on the reflex activity of spinal centers and on the cerebellar activity following vestibular stimulation were studied in cats. Succinylcholine decreased monosynaptic responses and increased polysynaptic discharges. The α -tubocurarine increased both monosynaptic and polysynaptic reflex responses initially; a few minutes after i.v. injection of the drug, a moderate decrease in the monosynaptic reflex response and a marked decrease in the polysynaptic discharges were observed. Cerebellar electrical activity, recorded from the flocculo nodular lobe, changed appreciably in cats after rotation in a centrifuge. The α -tubocurarine reduced this response, but succinylcholine increased it.

University of Milan
Milan, Italy

2785 University of Bonn. Natural toxic and narcotic compounds from plants. Final report, Tschesche, R., Bonn, Germany, July, 1962-30 June, 1963, 13 p. Contract DA-91-591-EUC-2580, unclassified report.

The chemical analyses of constituents isolated from plants showing toxic or other pharmacologically interesting properties are reported. The following plants were analyzed: Daphne mezereum (thymeleaceae), Ipomoea fistulosa (convolvulaceae), Iptadenia peregrina, Solanum siliambricatum (Solanaceae), Symplocos celastrea (symplocaceae), and Asclepias melleodora (asclepiadaceae).

University of Bonn
Bonn, Germany

2786 Laursen, T. & Svendsen, B. Borup. Glutamic pyruvic transaminase in the serum during treatment with chlorpromazine. Danish Medical Bulletin, 6(2):38-42, 1959.

The activity of the serum glutamic pyruvic transaminase (GPT) was investigated regularly in 58 psychiatric patients on chlorpromazine therapy and was compared with the results of other liver function tests in order to elucidate any warning reaction that might occur in cases of threatened jaundice. The transaminase activity was increased in 35 patients during the course of treatment. Chlorpromazine was withdrawn in four cases, because of pyrexia and two because of jaundice. Of these 23 patients, only 2 had received chlorpromazine previously, whereas 35 of the 35 patients, who showed normal GPT values, had received chlorpromazine previously. This indicates that patients with previous treatment react less violently to renewed treatment. In 12 out of the 35 patients who continued treatment with chlorpromazine despite raised GPT values, the transaminase values returned to normal, and none of these patients developed jaundice. The three other patients were discharged before the transaminase values had returned to normal, and these patients were not followed up. In the patients with raised GPT values, the results of the thymol turbidity test, zinc turbidity test, and cephalin-cholesterol-flocculation test were generally normal. It was concluded that GPT activity in the serum is too sensitive a reaction to estimate whether a patient will develop jaundice during chlorpromazine therapy.

University of Copenhagen
Copenhagen, Denmark

2787 Laursen, T. & Svendsen, B. Borup. The glutamic-pyruvic-transaminase and alkaline phosphatase levels in the serum during combined treatment with chlorpromazine and an antihistamine. Danish Medical Bulletin, 7(5):139-141, 1960.

An antihistamine, antistine, was investigated for its ability to provide protection against chlorpromazine jaundice in 83 psychiatric patients given chlorpromazine simultaneously with antistine at p.o. doses of 200 mg t.i.d. or injected doses of 100 mg t.i.d. The glutamic-pyruvic-transaminase (GPT) and alkaline phosphatase levels in the serum were determined prior to medication and once weekly during medication, and the values obtained were used as indicators of disturbances of liver function due to chlorpromazine. In 38 patients, treated for more than 1 month, with normal original values, 16 were found to have raised GPT values. In the 38 cases with normal original GPT values, it was found that 12 had raised alkaline phosphatase values. In the two groups with normal (22 patients) and raised (18 patients) GPT values that received chlorpromazine for more than 1 month, the average daily doses were 376 and 473 mg, respectively. This shows that a larger daily dose increased the risk of increased GPT values during treatment. The GPT value became normalized in 12 of 18 patients treated for more than 1 month. The alkaline phosphatase became normalized in 8 of the 13 patients treated for more than 1 month. Side effects (jaundice in 1 case, leucopenia in 3 cases, skin manifestations in 2 cases, intercurrent disease in 2 cases, and febrile reactions in 2 cases) necessitated drug withdrawal in 10 cases. It was concluded that the combination of chlorpromazine therapy with antihistamine cannot prevent transient disturbances of liver function that occur in about one-third of the patients during chlorpromazine therapy.

Rigshospitalet
University of Copenhagen
Copenhagen, Denmark

2788 Bülbing, Edith & Kuriyama, H. The effect of adrenaline on the smooth muscle of guinea-pig taenia coli in relation to the degree of stretch. Journal of Physiology, 169:198-212, 1963.

Changes produced by adrenaline on the membrane potential, membrane activity, and tension in stretched smooth muscle

preparations of the guinea-pig taenia coli are investigated. The guinea pigs weighed about 400 g. The conditions of stretch were defined by the W:L ratio—wet weight (mg)/length (mm)—which corresponds to the muscle's cross sectional area. The normal solution in all experiments was a modified Kreb's solution. The membrane potential varied with the degree of stretch. In the steady state, the maximum membrane potential occurred at a W:L ratio between 0.9 and 0.8. Following a sudden stretch, the membrane potential took longer than the tension to become steady and the time taken increased with the extent of the stretch. After a sudden release, membrane activity and tension were completely abolished and adaptation took as long as 5 minutes. Adrenaline (10^{-6} and 10^{-7}) applied during the steady state blocked the spike generation, increased the membrane potential, and caused hyperpolarization in all conditions of stretch. The highest membrane potential reached was at a W:L ratio corresponding to the optimum condition of stretch (W:L 0.9 to 0.8). The block of spike generation was more prolonged in unstretched than in stretched preparations. The effect of temperature was investigated at the W:L ratio of 0.75. The mean Q_{10} of the membrane potential between 22 and 32° C was 1.3. The mean Q_{10} of the spike parameters at this temperature range was spike height 1.2; rate of rise 2.8; rate of fall 2.4; and spike frequency 6.4. The hyperpolarization produced by adrenaline was less at 20° C than at 36° C at every degree of stretch. Resting tension (period when activity was suppressed by adrenaline) and active tension were discussed. The active tension-length curve was affected by temperature, but the resting curve was not affected.

Department of Pharmacology
University of Oxford
Oxford, England

- 2789 Bülbring, Edith & Kuriyama, H.
Effects of changes in ionic environment on the action of acetylcholine and adrenaline on the smooth muscle cells of guinea-pig taenia coli. *Journal of Physiology*, 166:59-74, 1963.

This work was undertaken to determine the effects of changes in ionic permeability of the smooth muscle membrane on the action of acetylcholine and adrenaline on the smooth muscle cells of guinea-pig taenia coli. Acetylcholine and adrenaline were injected into the bathing solution so as to produce a concentration of 10^{-6} and 10^{-7}

M, respectively. The degree of depolarization caused by acetylcholine depended on the initial membrane potential prevailing at the time of application. In K^+ -free solution, the depolarization caused by acetylcholine was abolished. In Na^+ -free solution, acetylcholine did not accelerate the spike discharge but still depolarized the membrane. In Ca^{2+} -free solution, acetylcholine had no effect; in excess Ca^{2+} (7.5 mM) its effect was potentiated. The degree of membrane hyperpolarization caused by adrenaline depended on the membrane potential at the moment of administration, and no hyperpolarization was observed when the membrane potential was 65 to 70 mV. In K^+ -free solution after the membrane was hyperpolarized and all activity had ceased, adrenaline produced further hyperpolarization. Adrenaline was ineffective in Ca^{2+} -free solution. In Na^+ -free solution, adrenaline had no effect; in Na^+ excess hyperpolarization caused by adrenaline solution. Chloride-deficient solution ($C_2H_5SO_3$) had little effect on the actions of either acetylcholine or adrenaline. These results indicate that acetylcholine exerts its effect by a nonselective increase of membrane permeability, whereas adrenaline affects the Na conductance during the active and resting state of the membrane, and modifies the movement of sodium across the membrane.

University of Oxford
Oxford, England

- 2790 Bargiel, Z. & Kadziela, W. Réaction vasomotrices du réseau vasculaire de l'oreille du lapin au cours de la fatigue aiguë sous l'influence de certaines substances neurovasotropes. (Vasomotor reactions of the vascular network of the rabbit ear during acute fatigue under the influence of certain neurovasotropic substances.) *Journal de Physiologie*, 55:192-193, 1963.

The effects of certain neurovasotropic drugs on the vasomotor reactions of fatigued and normal rabbits were investigated. The experiment involved 22 rabbits in which the variations of rhythm and amplitude in the vessels of the ear were recorded by a photoelectric cell with the aid of an electroencephalograph. Fatigued rabbits showed an increase in blood pressure, heart rate, and respiratory rate as compared with normal rabbits. In normal rabbits, adrenaline (0.5 mg) and acetylcholine (0.02 g) produced effects similar to those produced by fatigue, whereas serotonin (3.25 mg) produced vasodilation with a reduction of heart rate,

ollowed by prolonged vasoconstriction. Chlorpromazine (25 mg) decreased blood pressure, heart rate, and respiratory rate, whereas caffeine (0.2 g) increased these factors while inducing alternating vasodilation and vasoconstriction. Adrenaline and acetylcholine produced no significant changes in fatigued animals, whereas serotonin prolonged fatigue-induced vasodilation. Chlorpromazine blocked the vascular, cardiac, and respiratory effects of fatigue, and caffeine augmented these effects. These results indicate that both the central regulatory system and certain localized factors (humoral and myoneural) influence the action of the vascular network, but the latter factors tend to maintain the hemodynamic equilibrium of the vascular system.

University of Torun
Torun, Poland

2791 Keeler, M. H. Inter-relations of the effects of psilocybin on subjective sensation, photopic critical frequency of fusion, and circulating un-esterified fatty acids. *Experientia*, 19(1):37-38, 1963.

subjective response, critical fusion of frequency (CFF), and free fatty acid (FFA) levels were determined before and at half-hourly intervals for 4 hours after administration of psilocybin. Two subjects received 0.05 mg/kg psilocybin, and five subjects received 0.2 mg/kg psilocybin (the usual psychotomimetic dose). Subjective response was determined by the item checklist of Abramson (1959). A Mass Photic Stimulator was used to generate the CFF stimuli. The FFA levels were determined by the method of Dole (1956). Changes in subjective response and CFF were fairly, but not precisely, consistent, suggesting that the subjective drug effect and CFF may reflect similar basic processes. In one subject who received a small dose of psilocybin, CFF increased in the absence of a definite subjective response. In one subject, FFA did not increase during a marked drug response. In another subject, FFA increased only after the other drug effects were waning or gone. This suggests that a definite psilocybin response can occur without a simultaneous increase in circulating epinephrine and norepinephrine.

University of North Carolina
School of Medicine
Chapel Hill, North Carolina

2792 Kato, R., Frontino, G., & Vassanelli, P. Decreased activities of liver microsomal drug-metabolizing enzymes in the rats bearing Walker carcinosarcoma. *Experientia*, 19(1):31-32, 1963.

An experiment was conducted to investigate the activity of the liver microsomal enzymes that are responsible for the metabolism of hexobarbital, strychnine, and meprobamate in eight male rats with Walker carcinosarcoma 256. The rats were of the Sprague-Dawley strain, about 200 g in weight. The rats were inoculated s.c. with Walker carcinosarcoma 256 in the lateral abdominal region. Twenty-two days after inoculation, the rats were killed. The enzyme activities were determined by measuring the metabolized hexobarbital (conc. 6×10^{-4} M), strychnine (conc. 2×10^{-4} M), and meprobamate (conc. 3×10^{-4} M) by a liver microsomal preparation during 1-hour incubation. The liver was homogenized in three parts of isotonic KCl (1.15%), and the nuclei and mitochondria were sedimented by centrifugation of the homogenate. The incubation mixture contained 3 ml of the microsome-containing supernatant. Results of the experiment were determined by a comparison of the tumor-bearing rats with eight control rats. The metabolism of hexobarbital, strychnine, and meprobamate were significantly decreased in the liver of the tumor-bearing rats—hexobarbital metabolism decreased 53%, strychnine metabolism decreased 32%, and meprobamate metabolism decreased 46%. The results indicated that tumor-bearing rats are somewhat more sensitive to some drugs than are normal rats. This fact must be considered in cancer chemotherapy.

Institute of Pharmacology
University of Milan
Milan, Italy

2793 Hori, H. (A study of serotonin induced gastric hemorrhage in noradrenaline premedicated rats. II. The effect by various drugs in light of central depressant. Adrenaline synergic substances, adrenaline and serotonin metabolism related substances and lipid-amines.) *Folia Pharmacologica Japonica*, 58:11-19, 1962.

To understand the mechanism of gastric hemorrhage in noradrenaline-pretreated rats given 5HT, the effects of a wide variety of drugs on the development of gastric hemorrhage were analyzed. In one series of experiments, noradrenaline pretreatment was replaced by pretreatment with tyrosine, DOPA, dopamine, phenylethylamine, tyramine,

phenylalanine, ephedrine, hordenine, neosynesine, phenylethanolamine, methylamine, ethylamine, isopropylamine, butylamine, hexylamine, and octylamine. When 5HT was injected, all compounds produced hemorrhage, although certain of the drugs produced only a weak response. In another series of experiments, 5HT was replaced by tryptophane, 5HTP, 5HIAA, kynurenine, and bufotenine in noradrenaline-pretreated animals. The intensity of hemorrhage was low compared with that produced by 5HT. In the last series of experiments, the following drugs were given, along with noradrenaline and 5HT: (1) the central depressants urethane, chloralose, phenobarbital, morphine, chlorpromazine, and myanesine; (2) the ganglion-blocking agents hexamethonium and tetraethylammonium chloride; (3) the antispasmodics atropine and papaverine; (4) the antiadrenaline agents ergotamine, dibenamine, phentolamine, and tolazoline; (5) histamine and the anti-histaminic diphenhydramine; and (6) adrenaline-synergistic agents cocaine, ephedrine, sparteine, atropine, and strychnine. Results for each drug are discussed.

Chiba University
Chiba, Japan

2794 Hori, H. (A study of serotonin induced gastric hemorrhage in noradrenaline premedicated rats. I. Observations of 2, 3 conditions in gastric hemorrhage.) *Folia Pharmacologica Japonica*, 58:1-10, 1962.

When serotonin was administered to the rat, following premedication with noradrenaline, severe hemorrhagic ulcers were observed in the fundus of stomach. The most severe hemorrhage occurred when 20 µg/kg of noradrenaline (NA) and 10 mg/kg of serotonin (5HT) were administered at 30-minute intervals. The tendency to hemorrhage became weaker when the intervals between drug administration were 60 minutes, 120 minutes, or more. When the interval was shortened to 15 minutes, the hemorrhagic tendency was markedly decreased. Circulation disturbance due to blood pressure change induced by NA and 5HT was considered to be one of the important factors in the development of hemorrhage. It was shown that the heavier the weight of the subject, the easier the development of hemorrhage. Also less hemorrhagic tendency was observed in a group that was fasted for 48 hours before the experiment. The effect of hemorrhage of different types of food indicated that hemorrhage was affected little by adding vegetables to the diet, but the

intake of solid food, particularly dried fish and water, increased the hemorrhage. Premedication with methylmethionine sulfonium chloride, extracted from cabbage, suppresses the tendency to hemorrhage. The effect of temperature was studied, and it was noted that hemorrhage was most severe when the rats were fed at a room temperature of 20° to 22° C. The tendency was diminished by reducing the temperature to 15° to 18° C or to 8° to 10° C, or by increasing it to 28° to 30° C. The effects of the method of administering the drugs revealed that i. administration caused the most severe hemorrhage, which was decreased with i.p. injections, followed by a further decrease with s.c. injections. When NA and 5HT were given to adrenalectomized rats, the stomach hemorrhage reached the deeper part of mucosa; the degree of hemorrhage was more intense; and apparent edema of mucosa and muscle layer was noticed.

Chiba University
Kenku Bu, Japan

2795 Reyneir, M. Action du 4-hydroxybutyrate de sodium et de la cysteamine sur l'activité électrocardiographique chez la souris curarisée. (Action of sodium 4-hydroxybutyrate and cysteamine on electrocardiographic activity in the curarized mouse.) *Agressologie*, 4(3):245-250, 1963.

The effect of 4-hydroxybutyrate sodium (γ-OH) and cysteamine on ECG activity was studied in mice curarized with gallamine triethiodide or succinylcholine. Cysteamine and γ-OH were injected i.p. 30 minutes before curarization in doses of 25 mg/kg and 250 mg/kg, respectively. Gallamine and succinylcholine were given in doses of 250 mg/kg and 100 mg/kg, respectively. In mice curarized with gallamine, γ-OH significantly increased curarization time (time between injection of curare and the moment when the animal no longer exhibits contraction of thoracic and abdominal muscles). There was no significant difference in curarization time of mice given γ-OH alone and mice given γ-OH plus cysteamine. The ECG activation time (time from curare injection to disappearance of complex ECG) was significantly increased in mice given γ-OH; a further increase was seen in mice given γ-OH plus cysteamine. In mice given succinylcholine, the curarization time and the ECG activation time were increased by γ-OH.

Sainte-Anne Maritime Hospital
Toulon, France

2796 Drouet, J. & Laborit, H. Action de l'acide γ -amino-butérique et du γ -hydroxybutyrate de sodium sur le réflexe monosynaptique. (Action of γ -aminobutyric acid and sodium γ -hydroxybutyrate on the monosynaptic reflex.) *Agressologie*, (2):153-156, 1963.

The effect of GABA and of 4-hydroxybutyrate sodium (γ -OH), applied locally on the medulla, on the amplitude of the muscular response of the monosynaptic knee-reflex was studied in 15 decerebrated rabbits. Each of the drugs (2 g/10 ml) was applied, and the monosynaptic reflex activity was studied by recording the extension movements of the hind legs in response to the excitation of the knee tendon. When studied in 29 experiments, GABA produced a transitory inhibition followed by a period of facilitation and then a gradual and long-lasting inhibition of the monosynaptic reflex. The γ -OH, studied in 54 experiments, produced a manifest inhibition of the monosynaptic reflex, but never a period of facilitation. It seems that γ -OH acts on two levels: on a monosynaptic interneurons, by reinforcing an inhibitory hyperpolarizing action, or on the "IA Fiber-Motoneuron," a synapse, by blocking the facilitatory action.

Hôpital Anne Maritime
Marseille, France

2797 Mivelaz, M. Le G-Tril, un tranquillisant à propriétés antitremoriques. (G-Tril, a tranquilizer with antitremor properties.) *Schweizer Archiv für Neurologie, Neurochirurgie und Psychiatrie*, 2:243-248, 1963.

A study was made of the tranquilizing and antitremor properties of G-Tril, 3-(γ -n-utoxy- β -carbamyloxypropyl)-5-phenyl-5-methylhexahydropyrimidine-2,4,6-one. The tranquilizing effects were investigated in 10 patients (33 males and 37 females, 17 to 83 years of age) with diagnoses of anxiety state (14 patients), psychopathy (9), mixed depression (12), endogenous depression (6), organic syndrome (12), and chronic alcoholism (17). The drug produced good results in 30 patients, moderate improvement in 25 patients, and no change in 15 patients. Due to a previous discovery that G-Tril (300 mg/day) eliminated tremor when given to an alcoholic with anxiety and intense digital tremor, G-Tril was given to 34 patients with tremor due to alcoholism (17 patients), senility and Parkinson's disease (5 cases), emotional

disturbance (6 cases), and the effect of imipramine treatment (6 cases). Good results were obtained in all 17 alcoholics. In the senile and parkinsonian cases, good results were obtained in three, moderate improvement in one, and no change in one. In the emotionally disturbed, the drug produced good results in one, moderate improvement in three, and no change in one. Moderate improvement was obtained in four patients with the imipramine side effect, and no change occurred in two patients. The G-Tril was well tolerated, and the dosage that appeared to be best adapted to outpatient treatment was about 100 mg t.i.d. Drowsiness appeared at doses exceeding 400 mg/day.

(No address)

2798 von Euler, U. S. & Lishajko, F. Effect of reserpine on the release of catecholamines from isolated nerve and chromaffin cell granules. *Acta Physiologica Scandinavica*, 52:137-145, 1961.

The effect of reserpine on the release of catecholamines from isolated bovine splenic-nerve granules and rabbit and cat chromaffin-cell granules was investigated. Reserpine (10^{-8} to 10^{-5} M) strongly inhibited the spontaneous release of noradrenaline from bovine splenic-nerve granules. The catecholamine-releasing action of tyramine on nerve granules was unaffected by low concentrations of reserpine ($10 \mu\text{g/ml}$ when the suspension was varied between pH 6 and pH 7), but was almost blocked by 10^{-5} M of reserpine. Reserpine (1.6×10^{-5} M) was less active as an inhibitor on rabbit medullary granules and still less on cat medullary granules. The spontaneous release occurred at a lower rate in rabbit's medullary granules than in those from the cat. After administration of DOPA (100 mg/kg i.v.) in the rabbit, the rate of release from the medullary granules was greatly enhanced.

Department of Physiology
Karolinska Institute
Stockholm, Sweden

2799 Bertler, Åke, Hall, Gösta, Hillarp, Nils-Åke, & Rosengren, Evald. Uptake of dopamine by the storage granules of the adrenal medulla in vitro. *Acta Physiologica Scandinavica*, 52:167-170, 1961.

Isolated amine granules from the cow adrenal medulla were suspended in a solution of dopamine HCl ($10 \mu\text{moles/ml}$ to $20 \mu\text{moles/ml}$)

containing ascorbic acid 20 μ moles/ml, potassium chloride 40 μ moles/ml, magnesium chloride 5 μ moles/ml, sodium phosphate 15 μ moles/ml, and sucrose 180 μ moles/ml. Incubation was performed at +31° C for 1 hour, followed by chilling to 0° C. Large amounts of dopamine were regularly recovered in the granule sediment after an incubation at +31° C for 1 hour. At 0° C, only small amounts, if any, of dopamine were incorporated. The experiments demonstrated that at +31° C, the granules are capable of accumulating dopamine, even against an apparent concentration gradient. Even when large amounts of dopamine were incorporated in the granules, a decrease in the total amount of stored amines was usually observed.

Departments of Pharmacology and Histology
University of Lund
Lund, Sweden

2800 Decsi, L. & Nádor, K. Die Pharmakologie von *N*-Allyl-nor-atropin. (The pharmacology of *N*-allyl-noratropine.) Arzneimittel-Forschung, 13(7):567-571, 1963.

The pharmacological effects of *N*-allyl-noratropine (NANA) are described, with special regard to CNS activity. The following effects were determined: sedative effect in mice; central damping effect in mice; potentiation of anesthesia in mice; anticonvulsant effect in mice; antitremorine effect in pregnant mice; muscle relaxant effect in rats; effect on body temperature in rats; analgesic effect in mice and rats; effect on cat EEG; effect on cat conditioned reflex; effect on animal behavior in mice and rats; cholinolytic, adrenolytic, antihistaminic, antiserotonin, and spasmolytic effects; blood pressure variation in dogs and cats; effect on heart muscle contractility; effect on respiration in rabbits; acute toxicity in mice and rats; and semichronic toxicity in rats. The NANA has an analgesic effect stronger than that of morphine. It possesses many atropine-like qualities, but shows no substantial antagonism to tremorine. The possibility that NANA can be regarded as a hallucinogenic is discussed.

Pharmacological Institute
Medical University
Pecs, Hungary

2801 Sandberg, Finn. A new type of potentiating agents: 1-Benzyl-3- β -(subst. amino)-ethyl-5,5-dialkyl-substituted 2,4,6-trioxo-hexahydropyrimidine derivatives. Arzneimittel-Forschung, 13(7):530-534, 1963.

A series of eight benzyl-3- β -(substituted amino)-ethyl-5,5-dialkyl-substituted 2,4,6-trioxo-hexahydropyrimidine derivatives were synthesized and tested for their pharmacological activity. The derivatives were divided into three groups according to structure. Group I, four tertiary amines, were substituted pyrimidines containing the β -diethyl-aminoethyl or β -dimethylaminoethyl group as the basic radical in the 3-position and varying substituents in the 5-position. Group II, two tertiary amines, were derivatives with the basic radical in the 3-position containing the nitrogen in different heterocyclic groups, and having the same radicals in the 5-position. Group III, two quaternary amines (methyl iodides of their corresponding tertiary amines), had substituent groups in the 5-position. The following pharmacological tests were performed: potentiation of anesthesia in rats; potentiation of alcohol effects in mice; locomotor activity in mice; effect on body temperature in rats; autonomic effects in urethane-anesthetized rabbits and on guinea-pig ileum; and acute toxicity in mice. The tertiary amines potentiated anesthesia and, to some degree, the effects of alcohol. The quaternary amines produced no potentiation. None of the compounds had hypnotic activity, but in high doses, they had some ataractic action. All of the derivatives produced a moderate fall in body temperature and blood pressure, which were unaffected by atropine, antihistaminic or vagotomy.

Kungl. Pharmaceutical Institute
Stockholm, Sweden

2802 Mil'shteyn, G. I., Urmancheyeva, T. G., & Fufacheva, A. A. Vliyaniye dietilamida lizerginovoy kisloty na elektricheskuyu aktivnost' kory golovnogo mozga i nekotorykh podkorkovykh obrazovaniy u obez'yan. (Effect of lysergic acid diethylamine on electrical activity of the cerebral cortex and of certain subcortical formations in monkeys.) Fiziologicheskii Zhurnal SSSR imeni I. M. Sechenova, 49:173-180, 1963.

The effect of LSD on electrical activity of the brain cortex and of subcortical formations was studied in 6 rhesus monkeys (2 to 4 years of age). Electrodes were

placed under the skin in the frontal, occipital, and parietal areas of the head. Electrodes were also inserted in the corpus caudatus area to monitor electrical activity of the subcortical formations. A sinusoidal electrical current with a 50-cycle frequency was used as the stimulus. The LSD in doses of 10 μ g and 40 μ g produced a significant depression of electrical activity in the brain of the monkey. The LSD in a 10-mg/kg dose did not lead to a noticeable change in electrical activity of the corpus caudatus, tegument, globus pallidus, hypothalamus, and optic thalamus. An increased dosage of LSD (40 mg/kg) decreased phonic electrical activity and the appearance of regular outbreaks of hypersynchronized activity, which was clearly expressed in structures of the triopallid system. Excitability of the triopallid system under the influence of LSD (40 mg/kg) was somewhat lowered, but excitability of the thalamus and hypothalamus area did not noticeably change.

Institute of Experimental
Pathology and Therapy
Academy of Medical Sciences
Makhumi, U.S.S.R.

2803 Szirmai, E. *Pharmakologische und therapeutische Untersuchungen mit dem neuen Chinazolonderivat, dem Nitromethaqualon. (Pharmacological and clinical studies on nitromethaqualone -methyl-3-(4'-nitro-2'-methoxyphenyl)-quinazoline-(4)).* Therapeutische Umschau, 20(11):542-546, 1963.

A new quinazoline derivative, nitromethaqualone (NM), the chemical structure being -methyl-3-(4'-nitro-2'-methoxyphenyl)-quinazoline-(4), was subjected to pharmacological and clinical studies. The tests of acute toxicity in mice showed NM to have less than one-half the toxicity of methaqualone. No pathological effects were found when NM was fed for 3 to 5 months to rats, rabbits, and cats. The NM was considerably more effective than methaqualone in producing sedation, sleep, and narcosis; in depressing motility in mice; in anticonvulsive action; in damping the stimulating effect of caffeine; and in analgesic action. The test drug did not: (1) potentiate the action of barbiturates; (2) prolong strychnine convulsions; nor (3) depress food pressure. No teratogenic effects were produced by NM in rats and dogs. Administration of the drug to two successive generations of rabbits produced no

abnormalities. Comparison of the lethal dose with the effective dose indicates that the new hypnotic has a much broader therapeutic range than all other known hypnotics. In clinical tests of 60 patients with insomnia, NM produced sleep in 5 cancerous and 10 rheumatic patients, and in 39 of 45 patients with insomnia due to neurocirculatory conditions, fatigue, or toothache. No morning headaches were reported. Doses of 50 to 75 mg p.o. produced forced sleep in patients, but 200 to 400 mg/kg methaqualone did not.

Stuttgart, Germany

2804 Dmitriyev, L. I. *O terapevticheskom mekhanizme deystviya reserpina pri katatonicheskoy stuporoznoy forme shizofrenii. (On the therapeutic mechanism of the effect of reserpine in the catatonic stuporous form of schizophrenia.) Zhurnal Nevropatologii i Psikhatrii imeni S.S. Korsakova, 63(1):103-107, 1963.*

The action of reserpine was investigated in 15 patients (20 to 40 years of age) who had catatonic schizophrenia and were in a stuporous state. The duration of illness varied from 1 to 7 years. The effect of reserpine was studied, after three distinct periods: period 1, 20 to 40 days; period 2, 4 to 6 weeks; and period 3, 8 to 12 weeks. All patients were injected with reserpine i.p. During the first period, the patients received the drug in average doses of 3 to 5 mg/day; maximum dosage was 12 mg/day. Reserpine in average doses enhanced the inhibition of unconditioned reactions; higher doses intensified the inhibition and prolonged it. During the second period, the drug was given in doses ranging from 0.5 to 2.5 mg/day. Low doses of reserpine (0.5 to 1 mg) caused no changes in the neurodynamics of the patients; higher doses of 2.5 mg/day produced a stimulating effect on the unconditioned reactions, and increased cortical excitability within 1½ hours. Some patients who exhibited symptoms of parkinsonism were given tropacin in doses of 0.015 to 0.03 g b.i.d. or t.i.d. During the third period, low doses of reserpine (1 to 2 mg) produced a remission of the stupor in some cases; in other cases, a recurrence of the stuporous state was noted.

Institute of Higher Nerve Activity
Moscow, U.S.S.R.

2805 Dell'Omodarme, G. **Valutazione al test di Siegmund del potere antidolorifico di alcuni farmaci.** (Evaluation of the Siegmund test of the analgesic power of several drugs. *Archivio Italiano di Scienze Farmacologiche*, 13:167-169, 1963.

The efficacy of the Siegmund test (modified) in evaluating the analgesic potency of drugs was tested in 105 mice. The effect of the drugs (pyramidone, 25 to 100 mg/kg; pyridone, 15 to 100 mg/kg; phenylbutazone, 50 to 200 mg/kg; caffeine, 2.5 to 10.0 mg/kg; and chlormethazone, 25 to 100 mg/kg) on the "squirming" response in mice, produced by i.p. injection of 0.25 ml of 0.02% *p*-phenylquinone in 5% ethyl alcohol, was evaluated. The drugs to be tested were administered p.o. 1 hour before *p*-phenylquinone. With pyramidone, pyridone, and phenylbutazone, it was possible to demonstrate not only the analgesic effect but also the existence of a logarithmic ratio of the dose to the intensity of the effect. Simple graphic interpolation produced the following ED₅₀'s: pyridone, 39.8 mg/kg; pyramidone, 56.2 mg/kg; and phenylbutazone, 89.1 mg/kg. It was not possible to show dose-dependent effects for caffeine and for chlormethazone. It was concluded that the modified Siegmund test makes possible more precise evaluation of the analgesic potency of drugs.

Research Laboratory
Guidotti and Company
Pisa, Italy

2806 Manni, C., Trifogli, R., & Mazzoni, P. **Esperienze cliniche con una nuova tecnica di anestesia generale: la "neuroleptoanalgesia."** (Clinical experience with a new general anesthesia technique: Neuroleptanalgesia.) *Policlinico; Sezione Pratica*, 70(27):961-972, 1963.

A technique for general anesthesia employing dehydrobenzperidol (R 4749), a butyrophenone with neuroleptic action, and phentanyll (R 4263), a drug similar to morphine, is described, based on clinical experience with 300 surgery cases. The pharmacological effects of R 4749 and R 4263 are briefly discussed. The anesthetic procedure consisted of premedication with 5 to 10 mg R 4749 i.m. combined with 1.25 mg isopropamide i.m. 30 minutes before the operation; anesthesia was then induced with 25 to 30 mg R 4749 and 0.3 to 0.4 mg R 4263 i.v. Anesthesia was maintained with a nitrous oxide-oxygen mixture. When no premedication was given, anesthesia was induced with

40 to 50 mg R 4749 and 0.5 mg R 4263, followed by tubocurarine or succinylcholine. Maximal dosage of the two drugs for 4- to 5-hour operations was 1.3 mg R 4263 and 90 mg R 4749. The indications and contraindications for neuroleptanalgesia, such as that described with R 4749 and R 4263, are discussed.

Institute of General Clinical Surgery
and Surgical Therapy
University of Rome
Rome, Italy

2807 Wurmbach, Hermann. **Untersuchungen über die Wirkung von 3-Methyl-3,4-dihydroxy-4-phenyl-butin-1 (Substanz Kö 339) auf Hühnerembryonen.** (Studies on the effect of 3-methyl-3,4-dihydroxy-4-phenylbutine-1 (substance Kö 339) on chick embryos.) *Aerztliche Forschung*, 17(7):383-391, 1963.

The effects of Centalun (3-methyl-3,4-dihydroxy-4-phenylbutine-1) on developing chick embryos are reported. The eggs were injected with various doses of Centalun between the second and eighth days of incubation; 100 eggs were injected with 3% to 5% Centalun and 300 were injected with 7% Centalun in the air sac or in the yolk. Normal doses of the drug not only produced no damage, but decreased the fatality and malformation ratio; this effect was related to hyperemia in the yolk and allantoic circulation. Drug application after formation of the allantochorion led to local blood-vessel disturbance and formation of thrombi corresponding to local excessive concentrations of the drug. High doses injected into the yolk led to increased mortality and malformation ratios. Centalun, however, apparently caused no specific or accumulated unspecific malformations. Voluntary and involuntary musculature was normal, and reactivity to light and heat was intact. Histological examination of various organs indicated no specific damage.

Zoological Institute
University of Bonn
Bonn, Germany

2808 Davies, Brian M. **Phencyclidine: Its use in psychiatry.** In: Crockett, Richard, Sandison, R. A., & Walk, Alexander, eds. *Hallucinogenic drugs and their psychotherapeutic use.* Proceedings of the Royal Medico-Psychological Association. February 1961. Springfield, Illinois, Charles C. Thomas, 1963. Second session, p. 42-57.

The use of phencyclidine in the treatment of severe neurosis is described. The drug was given i.v. to 12 normal volunteers, and their responses to the drug are summarized. Acute symptoms last 45 to 60 minutes; the subject remains listless, unsteady, and, perhaps, nauseated for another hour or two. Six patients with long-standing neurotic illnesses were then treated with i.v. phencyclidine. These patients were given two sessions with sodium amytal i.v. to accustom them to drug-assisted psychotherapy. After this, phencyclidine was given twice a week by slow injection; 1 mg was given the first session, and the dose was increased by .5 mg to a maximum of 5 mg. Optimal dose was 3 to 5 mg given over a period of 3 to 5 minutes. The response to phencyclidine is compared with the response to LSD. Eight additional patients with obsessional states were given phencyclidine orally. The drug was given in a dose of 5 mg; dosage was increased to 7.5 or 10 mg at subsequent sessions. The responses were similar but less intense than those to i.v. phencyclidine. Further studies concerning the effectiveness of this drug in psychotherapy are recommended.

Bethlem Royal and Maudsley Hospitals
London, England

2809 Baker, Walter W. **Pharmacology of the central nervous system.** In: Siegel, E. A., ed. *Progress in neurology and psychiatry.* An annual review. Volume VII. New York, Grune & Stratton, 1962, p. 101-127.

A survey of the research and literature in the area of neuropsychopharmacology was presented. The survey included experimental and clinical papers offering information about the developments in psychopharmacology. The current status of the psychotropic drugs was appraised clinically, and the basic and clinical pharmacotherapy of psychotropic drugs was integrated. The following classification of drugs were discussed: ataraxic drugs, depressants and analeptics, CNS stimulants, central neurohumoral agents,

psychotomimetics, analgesic and anesthetic agents, anticonvulsants, and drugs used in hyperkinetic disorders. (279 references)

Temple University
School of Medicine
Philadelphia, Pennsylvania

2810 Bozzi, R., Allegranza, A., & Bruno, A. **Effetti del trattamento con reserpina, clorpromazina, haloperidol, elettroshock sulla eliminazione urinaria dell'acido 5-HIAA in schizofrenici. Correlazioni clinico - biologiche.** (Effects of treatment with reserpine, chlorpromazine, haloperidol, and electroshock on the urinary elimination of 5-hydroxyindoleacetic acid in schizophrenics. Clinico-biological correlations.) *Rivista di Patologia Nervosa e Mentale*, 84:49-75, 1963.

The urinary elimination of 5HIAA was determined in normal subjects and in schizophrenics, both with and without drug therapy or ECT. Sixty-two schizophrenics (39 paranoid, 10 catatonic, 7 hebephrenic, and 6 simplex) who were receiving no drug treatment or ECT, 48 schizophrenics (25 acute, 23 chronic) who were receiving drugs or ECT, and 30 normal controls were used for the determinations. Of the 48 patients receiving treatment, 12 were given reserpine, half receiving 3.8 mg/day and half receiving 8 mg/day; 12 were given chlorpromazine, half receiving 300 to 500 mg/day (average, 350 mg) and half receiving high doses averaging 800 mg/day; 12 were given haloperidol, half receiving 4 to 6 mg/day (average, 4.2 mg) and half receiving 8.1 mg/day; and 12 were given ECT, half receiving 5 treatments and half receiving 9 treatments. The duration of treatment was 15 to 22 days. Drugs were given i.m. for the first week and orally thereafter. No statistically significant difference was found between the urinary elimination of 5HIAA by normals and by schizophrenics receiving no drug treatment or ECT. Of the four treatments studied, only reserpine produced a highly significant increase in 5HIAA elimination. No relation was found between 5HIAA elimination and therapeutic effect.

Provincial Psychiatric Institute
Milan, Italy

2811 Nakamura, Keiji, Masuda, Yoshinobu, Tatsumi, Hiroshi, & Fujimoto, Katsuro. **Structure and activity relationship of monoamine oxidase inhibitors, phenylacetylhydrazide derivatives.** Japanese Journal of Pharmacology, 13:186-194, 1963.

The structure-activity relationship of new MAO inhibitors, 14 phenylacetylhydrazide derivatives, including P-5307 (*N*-benzyl-*N'*-phenylacetylhydrazide), is presented by the use of iproniazid and phenylisopropylhydrazine (JB-516) as control. Brain and liver enzyme preparations from male Wistar rats and male mice (DD strain) were used in the experiments. Substitutions of one hydrogen at the terminal amino nitrogen in the molecule increased the inhibitory effect, whereas substitution of the hydrogen α -carbon of phenylacetylhydrazide decreased the MAO inhibitory activity. Comparative studies of the inhibitory effect and CNS effect of P-5307 were also carried out. The mitochondrial enzyme was suppressed by P-5307 and iproniazid more than that of the original homogenates. The inhibitory effect of JB-516 on both MAO preparations was the same. The liver homogenate was more sensitive to P-5307 and iproniazid than the brain homogenate, whereas with JB-516 there was no marked difference in sensitivity. The duration of the MAO inhibitory effect of P-5307 (100 mg/kg i.p.), iproniazid (100 mg/kg i.p.), and JB-516 (30 mg/kg i.p.) was longer in the brain than in the liver in vivo. Iproniazid (30 mg/kg), P-5307 (30 mg/kg), and JB-516 (5 mg/kg) administered s.c. daily for 5 weeks produced an increase in brain noradrenaline. The effects of the compounds (at dosages of 10, 25, 50, and 100 mg/kg) on spontaneous and forced motor activity in mice were studied by using the photocell cage and rotating cylinder. The JB-516 caused a marked increase in spontaneous activity, but there was no significant difference in the responses of the animals to the three compounds in the rotating cylinder. Pretreatment with P-5307 and JB-516 did not induce sleep in animals treated with 40 mg/kg of methylhexabital, but did potentiate (at 100 and 200 mg/kg) the effects of sleep produced by 80 mg/kg of methylhexabital. Pentylene-tetrazol-induced convulsions were slightly depressed by P-5307 and JB-516, which had no effect on electroshock convulsions. There was no correlation between MAO inhibitory activity and toxicity. The P-5307 proved the lowest toxicity in rats and mice. In the subacute toxicity studies of P-5307 and iproniazid (at doses of 5,

10, and 30 mg/kg) and JB-516 (1, 2, and 5 mg/kg), iproniazid and JB-516 caused slight liver damage.

Dainippon Pharmaceutical Company
Research Laboratories
Osaka, Japan

2812 Kalmykova, K. M. **Deystviye aminazina na vysshuyu nervnuyu deyatel'nost' i vazomotornye reaktsii sobak v usloviakh gipertireoidizatsii.** (Effect of Aminazine on the higher nervous activity and vasomotor reaction in dogs in hyperthyroidism.) Problemy Endokrinologii i Gormonoterapii, 9:25-28, 1963.

An experiment was conducted to study the action of chlorpromazine on higher nervous activity and vasomotor reactions in four sexually mature, male dogs with hyperthyroidism. Three of the dogs received 1 g/1 kg/day of thyroindin and i.m. injections of chlorpromazine (1 mg/kg/day) for 2 to 3 months. After both a brief and a prolonged administration of chlorpromazine, certain reactions were noted. The general state of excitation was replaced by calmness and normalization of motor reactions. Reinforcement of the inhibitory process, restoration of differentiation, and reduction of positive reflexes (more pronounced after prolonged administration) were noted in higher nervous activity. The conditioned-reflex vasomotor reactions were diminished, "thyrogenic" hypertension was not observed. The arterial blood pressure normalized. Fifteen to 20 days after the cessation of chlorpromazine administration the drug's aftereffects continued, as manifested by vasomotor reactions. In dogs with hyperthyroidism, chlorpromazine has a stronger and more lasting effect than that of sodium bromide and of sodium amytal on higher nervous activity, as well as on the vasomotor disorders. Chlorpromazine can be used in the treatment of thyrotoxicosis.

The Ukrainian Institute of
Experimental Endocrinology
Ukraine, U.S.S.R.

2813 Sulser, H., Schwarz, K., & Schwarz, M.
Über Kreuzreaktionen bei experi-
menteller photoallergischer Chlorpromazin-
sensibilisierung. (On cross reactions in
experimental photoallergic chlorpromazine
sensitization.) *Dermatologica*, 127:108-
120, 1963.

Cross-reactions with various psychopharma-
cological agents were studied in albino
guinea pigs sensitized to chlorpromazine.
Chlorpromazine (10% in 70% alcohol) was
applied to a shaved neck area over a 3½-
week period; each animal received about
0.5 g chlorpromazine. Fourteen days after
the last administration, the guinea pigs
were tested for sensitization with 2% chlor-
promazine, chlorprothixene, and imipramine;
no reaction occurred. Sensitization to
chlorpromazine and ultraviolet light was
then attempted. Chlorpromazine (10%) was
applied to the shaved neck areas of guinea
pigs; the area was then exposed to ultra-
violet light until a local erythema was
noted. This process was repeated at 3- to
4-week intervals until the animals had
received 150 mg chlorpromazine. The addi-
tion of ultraviolet light induced sensitiza-
tion. Twenty-seven chlorpromazine-sensi-
tized guinea pigs were then tested with a
variety of compounds for cross-sensitization
reactions. Of the 27 animals, chlorpro-
thixene gave a positive response in 22,
imipramine in 16, amitriptyline in 12,
and chloramitriptyline in 14. The allergic
cross-reactions occurred independently of
irradiation. Results are tabulated.

Dermatological Clinic
University of Zurich
Zurich, Switzerland

2814 Hahn, R., Fruttero, F., &
Scarzella, R. Modificazioni
nell'adattamento uditivo per effetto di
farmaci ad azione sul sistema nervoso
centrale. (Changes in auditory adaptation
caused by drugs acting on the central
nervous system.) *Minerva Otorinolaring-
ologica*, 13:132-136, 1963.

Changes in auditory adaptation caused by
caffeine, bromide, and chlorpromazine were
tested in 10 normal subjects. The auditory
threshold for one ear was established for
each subject. The following two procedures
for auditory adaptation were used: (1)
measuring the time to exhaustion of the
auditory threshold when a tone of 4,000 cps
is presented to the same ear; (2) measuring
the time to exhaustion of the auditory

threshold when a continuous 30-db noise or
an intermittent (1 cps) 30-db noise is
presented to the opposite ear. The thresh-
old of hearing and auditory adaptation were
determined 10 and 30 minutes after 25 mg
caffeine p.o., 10 and 20 minutes after 1 g
bromide in solution i.v., and 2 hours after
50 mg chlorpromazine p.o. Interference
produced by acoustical stimuli to the
opposite ear was modified by the excitatory
action of caffeine and the sedative action
of bromide on the cortical centers, indicat-
ing that these cortical centers participate
in the mechanism of acoustical interference.
In a subject under normal conditions, the
time of auditory threshold exhaustion is
greater if a continuous noise is presented
to the opposite ear and is less if the noise
is intermittent. This relationship is
reversed by chlorpromazine and resembles
that occurring in patients with extrapyra-
midal diseases. The action of chlorproma-
zine appears to take place in the
mesencephalo-diencephalic area.

University of Torino
Torino, Italy

2815 Neyen, H. Chlorprothixen als
Antipruritusum in der Dermatologie.
(Chlorprothixene as an antipruritic agent
in dermatology.) *Medizinische Welt*,
19:1082-1084, 1963.

The use of chlorprothixene in the treatment
of 207 male patients, 12 to 85 years of
age, with pruritis is reported. Ninety-
seven outpatients were given 30 to 75 mg
chlorprothixene daily, and 110 inpatients
received 30 to 200 mg daily p.o. for 6
months. Daily dosage for outpatients did
not exceed 75 mg daily, because of the
possibility of orthostatic hypotension at
higher doses. Of the 207 patients, pruritis
was completely eliminated in 184 cases, and
23 cases were partially improved. Lympho-
penia and orthostatic hypotension were the
only side effects reported. The drug pro-
duced no toxic effects during the study.

Dermatological Clinic
University of Cologne
Cologne, Germany

2816 Gavend, M. & Gavend, M. R. Contribution à l'étude du mécanisme de l'action hypertensive de la β -phényl-ethylhydrazine (phenelzine). (Contribution to the study of the mechanism of the hypertensive action of β -phenylethylhydrazine (phenelzine).) Comptes Rendus des Séances de la Société de Biologie et de Ses Filiales, 157:579-582, 1963.

Modifications in phenelzine-induced hypertension (1 to 5 mg/kg phenelzine i.v.), produced by chlorpromazine (3 mg/kg i.v.), cocaine (5 mg/kg i.v.), and reserpine were studied in the chloralose-anesthetized dog. Reserpine was given s.c. in 3-mg/kg doses, 48 and 24 hours before experimentation. Tracings of the arterial pressure showed that phenelzine hypertension was considerably diminished by all three test drugs. The pressor response to phenelzine was restored by slow infusion of noradrenaline. Noradrenaline infusion did not modify phenelzine hypertension in animals who were not treated with the test drugs. The hypertensive action of phenelzine appeared to correspond to a sympathomimetic action exerted by an indirect mechanism, implying the mobilization of catecholamines.

Laboratory of Pharmacology
School of Medicine and Pharmacy
Marseille, France

2817 Delphaut, J. Recherches sur les effets de masse chez le Poisson Gambusia holbrooki. III. Action de la cocaine, de l'amobarbital et de la colchicine. (Research on the mass effects in the fish Gambusia holbrooki. III. Action of cocaine, amobarbital and colchicine.) Comptes Rendus des Séances de la Société de Biologie et de Ses Filiales, 157:577-579, 1963.

The ability of cocaine, amobarbital, and colchicine to display the "mass effect" in grouped fish (Gambusia holbrooki) was tested. Mass effect is defined as the decrease in toxicity of a compound when large groups are exposed simultaneously. Drug concentration were as follows: 16 to 40 mg/l amobarbital, and 1.25 to 5 mg/l colchicine. Fish were exposed singly and in groups of 10, 20, and 50 for each drug dose. Only cocaine displayed a mass effect. With the exception of barbiturates, compounds that display no mass effect usually exert little CNS action. Compounds that display mass action are, in general, psychomotor stimulants. Drugs previously observed for mass effect are discussed.

It was concluded that no simple relationship exists between pharmacological action and ability to produce the mass effect.

School of Medicine and Pharmacy
Marseille, France

2818 Himwich, Harold E., Brune, Guenter G., Steiner, William G., & Kohl, Herbert H. Chapter 18. A pharmacological study of terminal methyl groups in animals: (1) Electrophysiological analysis of chlorpromazine, imipramine, and amitriptyline, and their demethylated congeners; (2) Behavioral evaluations of chlorpromazine and its demethylated congeners in relation to brain concentrations of phenothiazines. Recent Advances in Biological Psychiatry, 6:196-207, 1963.

The significance of the dimethyl configuration in the pharmacological action of chlorpromazine, imipramine, and amitriptyline was determined by studying the action of these compounds and their demethylated congeners on EEG alerting produced by pain and sound stimulation. The action of chlorpromazine and its congeners were also studied on elevation of the threshold voltage for maximal recruitment and on behavior in relation to brain levels of phenothiazine. The electrophysiological studies were made in adult male New Zealand albino rabbits, weighing 2 to 3 kg. Behavioral studies were made in albino Wistar rats, weighing 300 to 400 g. Imipramine and amitriptyline were stronger, on a mg/kg basis, than their demethylated congeners, as shown by their ability to suppress alerting to pain. Consistent and marked differences in the pharmacological effectiveness of chlorpromazine, desmonomethyl chlorpromazine, and desdimethyl chlorpromazine were revealed by the measure employed. On a basis of brain phenothiazine levels, chlorpromazine was found to be two to three times more potent than desmonomethyl chlorpromazine in depressing behavioral reactivity, whereas desdimethyl chlorpromazine was the least active of the three compounds studied. Similar relationships between these three congeners were observed in the elevation of EEG recruitment thresholds following thalamic stimulation and for the blockade of the EEG alerting response to pain. From these findings, it may be concluded that the *N,N*-dimethyl configuration plays a major role in the

pharmacological effectiveness to chlorpromazine, and that progressive demethylation of this drug is associated with decreasing potency of action.

(No address)

2819 Oberbeckmann, Heinz. *Erfahrungsbericht über die Therapie der Depressionen mit einem neuen Antidepressivum.* (Report on experiences in the therapy of depression with a new antidepressive agent.) Deutsches Medizinisches Journal, 14(13):406-408, 1963.

The treatment of 36 female depressives with amitriptyline is reported. Diagnoses included 6 cases of involutional depression, 11 of depression associated with schizophrenia, 6 of agitated hypochondria associated with brain damage, and 3 of endogenous depression. Initial dosage of amitriptyline was 100 mg t.i.d.; maintenance dosage was 25 to 50 mg t.i.d. In some patients, amitriptyline therapy was combined with phenothiazine or thioxanthene derivatives. Amitriptyline caused some degree of improvement in all cases. Side effects included numbness, vertigo, nausea, and stupor; these reactions occurred initially, and subsided during the extended course of treatment. No extrapyramidal symptoms were observed. The therapeutic effect usually occurred 2½ to 3 weeks after initiation of treatment, but in some cases, a response was seen within 4 to 5 days. One case history is reviewed in detail.

Federal Hospital
Marsberg, Germany

2820 De Loose, F. *Expérimentation d'un nouveau dérivé de la phénothiazine (Dixyrazine).* (Experimentation with a new phenothiazine derivative (Dixyrazine).) Bruxelles-Médical, 43(23):671-677, 1963.

A report is given of experience with Dixyrazine [2-methyl-3-(1-hydroxyethoxy-4-piperazinyl)-propyl]-10 phenothiazine, in the treatment of a wide range of disorders. In 2 years of using Dixyrazine, no allergic responses have been noted, and only one akinetic response was seen; several patients complained of marked fatigue when walking. Initial dosage was usually 10 to 2.5 mg t.i.d. Doses of up to 25 mg q.i.d.

were well tolerated. Dixyrazine was used in the treatment of the following conditions: (1) severe weight loss; (2) hyperthyroidism; (3) cardiovascular disorders (10 sclerotic patients, 2 cases of arrhythmia); (4) respiratory disorders (one case of bronchial asthma with a marked psychic component); (5) gastrointestinal disorders (six patients with excess stomach acid with vomiting, two with gall bladder disorders, and four with spastic colitis); (6) neurovegetative dystonia (50 cases, mostly of the pseudohyperthyroid type); (7) hyperventilation syndrome; and (8) neoplasms. Dosage of the drug and its ability to induce weight gain and improvement in general condition are reported for each condition treated. Side effects included psychotic reaction with catatonic state in two patients, excessive fatigue in four patients, and subjective anorexia in three patients. The drug produced adequate weight gain in most of the conditions listed, and showed an extremely low toxicity.

Polyclinic
Ghent, Belgium

2821 Rytvinskiy, S. S. *Izmeneniya nekotorykh pokazateley vneshnego dykhaniya pod vliyaniyem aminazina i neuroplegicheskoy smesi pri legochnom tuberkuleze.* (Changes in various indices of external respiration under the action of a chlorpromazine-neuroplegic mixture in pulmonary tuberculosis.) Kazanskii Meditsinskii Zhurnal, 2:28-33, 1963.

The action of chlorpromazine alone and in combination with a neuroplegic mixture was investigated on the indices of external respiration in 35 patients with pulmonary tuberculosis prior to thoracic operations. The patients received the following combinations: 5 received the total mixture, which consisted of 2.5% chlorpromazine at 2 ml, 2% diphenhydramine at 2 ml, 2% trimeperidine at 2 ml, and 0.1% atropine at 1 ml; 5 received only 2 ml of diphenhydramine; 17 received only 1 ml chlorpromazine; and 8 patients received 2 ml chlorpromazine. The following external respiratory indices were determined: the frequency, depth, and minute volume of respiration; absorption of O₂; and the coefficient of the absorption of O₂. The patients were operated on within 1 to 1½ hours following the introduction of the mixture. The following results were obtained: an increase in the various indices occurred in one-third of the patients, whereas a

decrease in the indices occurred in two-thirds of the patients. The minute volume of respiration decreased. The frequency of respiration increased greatly 1 hour after the intake of the mixture; after 3 hours, the indices returned to normal. The depth of respiration decreased slightly (by one-fifth to one-sixth of the initial measure), and the minute volume decreased. In most of the patients, a decrease in the absorption of O_2 was noted, it being especially apparent 1 hour after the introduction of the mixture; the coefficient of absorption also decreased. Chlorpromazine alone had the same action on the indices as in combination with the mixture. The intake of chlorpromazine in combination with a neuroplegic mixture, in patients whose initial indices decreased, can produce an increase in the absorption of O_2 during surgery. Patients with severe dyspnea and an increased pulse beat should not be given chlorpromazine alone or in combination with a neuroplegic mixture during thoracic surgery.

The Kazan Tuberculate Hospital
Kazan, U.S.S.R.

2822 Imaizumi, Masahiro. (The effect of chlorpromazine on the variations of urinary excretion of catecholamines in ocular surgery of rabbits.) Journal of the Osaka City Medical Center, 12:91-95, 1963.

The effect of chlorpromazine on the variations in urinary excretion of catecholamines following ocular surgery was determined in nine male albino rabbits. The animals were divided into two groups; Group I received 10 mg/kg chlorpromazine s.c. 1 hour prior to surgery, and Group II received 10 mg/kg chlorpromazine s.c. 1 hour prior to surgery and 4 days after surgery. Adrenaline and noradrenaline were determined by the trihydroxyindole method after isolation by the catecholamines on Duolite C-25 exchange resin. Vanillylmandelic acid (VMA) was measured by the Imaizumi-Miyake method. Excretion in the nine test animals was compared with that of controls. Both test groups showed an increase in urinary excretion of catecholamines and VMA, 4 to 6 days after surgery, but the increase was less than that seen in control animals. Group II showed a smaller increase in urinary excretion of catecholamines and VMA

than did Group I. Chlorpromazine inhibited the postoperative increase in urinary catecholamine and VMA excretion.

Department of Ophthalmology
Osaka City University Graduate School
Osaka, Japan

2823 Kuebler, W. F., Jr. & Bendure, J. D. The effect of dimeflin on acute canine barbiturate depression. American Journal of Veterinary Research, 24(103):1227-1231, 1963.

Assessment of dimeflin (3-methyl-7-methoxy-8-dimethylaminomethyl flavone) without and combined with pentobarbital was based on recovery time, respiration rate, and pulse rate in 12 adult, mongrel dogs (4 males and 8 females). All solutions were given i.v. at a level of 1 cc/5 pounds of body weight. Recovery was evaluated by observing the drug effects on the seven clinical signs used by Maynert in assessing the degree of neurologic derangement in dogs. An extra-period Latin square change-over experimental design was used. The dogs varied greatly in their responses to pentobarbital. Because of this variability the 15% shortening of recovery time was judged to be too small to be of importance. The data suggest that the respiration rate induced by pentobarbital containing dimeflin may have been greater than that induced by pentobarbital alone, but the evidence was not convincing because of the large variability in response. In the early stages of anesthesia, the pulse rate was lowered 23%; both pulse and respiration rates were within normal limits. There were no drug carryover effects observed with the anesthetic solution given on five consecutive occasions with a lapse of 6 to 8 days between administrations. There was no evidence of drug toxicosis induced by the anesthetics in any of the dogs.

Research Laboratories
Jensen-Salsbery Laboratories
Division of Richardson-Merrell Inc.
Kansas City, Missouri

2824 Komor, Károly, Szechenyi Nagy, László, & Vagfalvy, Ilona. Chlorpromazin injectio után végzett alanyagcsere meghatározás és I^{131} tárolási görbe értékelése a pajzsmirigy működési állapotának megítélésére. (Determination of basal metabolism after chlorpromazine injection, and the I^{131} storage curve for evaluation of the functional state of the thyroid gland.) Magyar Belorvosi Archivum, 15:70-73, 1962.

See also: 2656, 2658, 2659, 2660, 2664, 2677, 2709, 2728, 2741, 2747, 2750, 2752, 2753, 2756, 2771, 2774, 2828, 2833

Three methods were evaluated for assessing thyroid function: I^{131} storage, basal metabolism following chlorpromazine administration, and measurement of serum cholesterol level of 109 patients. Determination of basal metabolism 1 hour after a dose of 25 mg chlorpromazine i.m. was concluded to be the best means of evaluating thyroid function.

Clinic B
Peterfy Sandor utca Hospital
Budapest, Hungary

2825 Mekhedova, A. Ya. Contribution to the problem of the effect of Meratran on the higher nervous activity of dogs. Report II. Administration of Meratran on the background of a neurotic state. Akademiia Meditsinskikh Nauk SSSR, 7:245-252, 1963.

Some of the properties of pipradrol were determined by evaluating the effect of various doses on the higher nervous activity of two dogs in a sustained neurotic state. One dog had an unbalanced nervous system, and the other dog had a weak nervous system. Pipradrol was given p.o. 1 hour before the experiments, usually performed once every 7 to 8 days. A 5-mg dose, administered to the dog with the unbalanced nervous system, resulted in transitory restoration of higher nervous activity, and an increase to 10 mg of pipradrol resulted in a return to a deep neurotic state. Administration of a 4 to 5 mg dose to the dog with the weak nervous system was followed by stable recovery of higher nervous activity. Doses of 0.0025 mg and 5 mg apparently enhanced excitation and improved conditioned reflex activity during the neurotic state. The fact that one dog's neurosis was successfully treated with pipradrol, whereas the other animal's disorders improved for a few days only, may be explained not only by the different typological traits of the experimental animals but also by the difference in the nature of their neuroses.

(No address)

BIOCHEMISTRY

2826 Lankenau Hospital. **Urinary elimination of catecholamines as an indication of stress response in man.** Final report, Rodahl, Kaare, Philadelphia, Pennsylvania, 1963, 30 p. Contract FA-2678, unclassified report.

In order to find an objective biochemical measure of fatigue caused by work stress of long duration, four healthy men (19 to 36 years of age) were subjected to four different types of work, during which time analyses of the blood, measurements of O_2 uptake and CO_2 output, measurements of metabolism, and analyses of the urine were made. During heavy work on the bicycle ergometer for 10 minutes, the O_2 uptake was 2.7 liters/minute in one subject working at 1,200 kmp/minute and 2.4 liters/minute in two subjects working at 1,050 kmp/minute. The blood lactic acid rose rapidly, the plasma free fatty acid (FFA) concentrations were 0.41 to 0.54 meq equivalents/liter, and the ratio of FFA/glucose was about 0.1. Due to the variations in urinary excretion of catecholamines, no conclusions could be drawn. During an intermittent run (5 seconds work, 5 seconds rest) at 7.5 miles/hour, there was no marked change except an eight-fold increase of the O_2 uptake. The urinary output of catecholamines was increased in only one subject. During continuous moderate work on the bicycle at 900 kmp/minute, two subjects showed markedly elevated blood lactate, all four subjects had a twofold to threefold increase of plasma FFA, the ratio FFA/glucose was 0.24 to 0.29, and the urinary excretion of catecholamines increased although the pattern varied from one subject to another. During light prolonged work, which consisted of five 1-hour work periods and four 15-minute rest periods, the O_2 uptake increased, the blood lactic acid level remained unchanged, the plasma FFA concentration increased, the blood sugar was fairly constant, and the urinary output of catecholamines increased with variation. These results indicate that the urinary output of catecholamines cannot be used as a practical index to estimate the work stress. The

ratio FFA/glucose in the blood seems to be a more reliable and sensitive index under standardized conditions.

Lankenau Hospital
Philadelphia, Pennsylvania

2827 University of Pennsylvania. **Neuro-humoral control of the pituitary.** Final report, McCann, Samuel McDonald, Philadelphia, Pennsylvania, 4 December, 1963, 6 p. Contract AF-AFOSR 62-133, unclassified report.

A final report on studies aimed at clarifying the hypothalamo-anterior hypophyseal interrelationship is presented. Results of the following experiments are summarized: (1) the effect of acute cold ($0^\circ C$) exposure on ACTH release in dogs; (2) the effects of implants of testosterone and estrogen into the hypothalamo-hypophyseal region on adrenal weight in rats; (3) a comparison of the regulation of luteinizing hormone (LH) in immature and adult rats; (4) location of the site of action of gonadal steroids in inhibiting LH release; (5) the action of hypothalamic LH-releasing factor (LH-RF); and (6) location of the site of action of estrogen in stimulating secretion of luteotrophin. A list of papers published as part of this project is appended.

Department of Physiology
University of Pennsylvania
School of Medicine
Philadelphia, Pennsylvania

2828 University of Pittsburgh. **Atropine detoxication during hypothermia by the isolated perfused rat liver.** Final report, Kalser, Sarah C., Pittsburgh, Pennsylvania, 2 October, 1963, 10 p. Grant AF-AFOSR 87-63, unclassified report

The metabolism of C^{14} atropine by the isolated, perfused rat liver under normothermic and hypothermic conditions was

studied. The half-life of atropine was prolonged under hypothermic conditions, and the percent of drug remaining in the plasma 4 hours after administration was greater at the low temperatures. Four hours after administration, liver perfused at 17.5° C secreted only 20% as much C¹⁴ into the bile as liver perfused at 37° C. At 25° C bile collected 4 hours after drug administration showed about 60% of the amount secreted at normothermic temperatures. At all temperatures, the material appearing in the bile was an altered form of atropine and none of the five chromatographically separable compounds was tropic acid. Biliary secretion of atropine metabolites by intact, nephrectomized rats was in agreement with data obtained from the isolated, perfused liver at 37° C and 25° C. At 17.5° C, the biliary secretion of atropine metabolites was greater by the perfused preparation than by the intact rat.

University of Pittsburgh
Pittsburgh, Pennsylvania

2829 University of Minnesota. **Alterations of brain biochemistry and development of behavior.** Shideman, F. E., Minneapolis, Minnesota, 1963, 9 p. Grant F-AFOSR 204-63.

variations in brain catecholamines and serotonin of embryonic and developing chickens and in brain catecholamines of the developing rat were measured. In the chick experiments, catecholamine concentrations in the optic lobes and the remainder of the brain were measured between 9 days before hatching and 29 days after hatching. Serotonin concentrations were measured only after hatching. The peak in catecholamine concentration occurred 4 to 6 days prior to hatching; the peak was more marked in the optic lobes. A second peak occurred in the optic lobes shortly after hatching (12 to 20 hours). Serotonin level in the optic lobes did not change significantly between days 1 and 25 after hatching. Between days 1 and 25, serotonin levels in these parts of the brain outside the optic lobes increase, until at day 25, the level is almost double that in the optic lobe. In the rat experiments, brain catecholamine levels were measured between birth and 28 days of age. There appeared to be two periods in the developing rat at which abrupt increases in total catecholamine

level occurred—between 1½ and 4 days after birth and between 24 and 28 days of age.

University of Minnesota
Minneapolis, Minnesota

2830 Smythies, J. R. **Section 4. Chemical aspects of the treatment of schizophrenia.** Springfield, Illinois, Charles C. Thomas, 1963, p. 56-60.

A discussion of the current chemical therapy of schizophrenia, based almost entirely upon the phenothiazine group of compounds, is presented. The phenothiazines were divided into three subgroups, according to whether the side chain at the nitrogen contained a dimethylaminopropane chain, a piperazine ring, or a piperidine ring. The results of experiments with chlorpromazine and reserpine are given, and the fact that these drugs have close connections with certain key chemicals in the brain, namely serotonin and norepinephrine, is discussed.

University of Edinburgh
Edinburgh, Scotland

2831 McBay, Arthur J. & Algeri, Elvera J. **Ataraxics and nonbarbiturate sedatives.** In: Stolman, Abraham, ed. Progress in chemical toxicology. Volume 1. New York, Academic Press, 1963, p. 157-187.

Methods for determining the following compounds in biological media are described: phenothiazine derivatives, *o*-propoxyphene, chlordiazepoxide, glutethimide, hydroxyzine, methapyrilene, ethchlorvynol, methyprylon, ethinamate, phenaglycodol, captodiamine, and imipramine. The metabolic fate of the phenothiazines, *o*-propoxyphene, glutethimide, methyprylon, ethinamate, and imipramine is also discussed.

Department of Legal Medicine
Harvard University Medical School
Boston, Massachusetts

2832 Yamamoto, Akira, Yoshimura, Hidetoshi, & Tsukamoto, Hisao. **Metabolism of drugs. XXIX. Metabolic fate of meprobamate. Further studies on the structure of the metabolites.** Chemical and Pharmaceutical Bulletin, 10(7):540-544, 1962.

From the results of paper chromatography, infrared spectroscopy, and color reactions, the structures of three metabolites isolated from the urine of rabbits and dogs that were administered meprobamate were identified as keto-meprobamate (2-methyl-2-(2-oxopropyl)-1,3-propanediol dicarbamate), hydroxymeprobamate (2-methyl-2-(2-hydroxy-propyl)-1,3-propanediol dicarbamate), and carboxymeprobamate (2-methyl-2-(2-carboxy-ethyl)-1,3-propanediol dicarbamate).

Institute of Pharmaceutical Sciences
Kyushu University
Katakasu, Fukuoka, Japan

2833 Del Mastro, S. **L'Insidon: Armonizzatore neurovegetativo e psichico. (Insidon: Neurovegetative and psychic tranquilizer.)** Bollettino Chimico-Farmaceutico, 102:85-87, 1963.

The literature on opipramol is reviewed as to its chemistry, and pharmacological testing as well as clinical experience with the drug. The compound is an iminostilbene derivative that produces no pathological organic modifications. It has biphasic action, consisting of an anxiolytic effect followed by a euthymic effect. Clinical documentation covering a total of 1,500 patients indicates the drug is therapeutically effective. The average dosage is 150 to 200 mg/day, for a period of not less than 2 weeks. Opipramol is well-tolerated, and has no significant side effects. The initial phase of its action may be accompanied by therapeutically insignificant drowsiness, tachycardia, and vertigo.

Milan, Italy

2834 Giurgea, M., Dauby, J., Levis, S., & Giurgea, C. **Un test antitétrabénazine modifié, pour le screening des produits antidépresseurs. (A modified antitetraabenazine test for screening antidepressive drugs.)** Medicina Experimentalis, 9(4):249-262, 1963.

An antitetraabenazine test is described for screening antidepressant compounds. Male rats, 150 g in weight, were given a test

compound s.c. 1 hour before injection of 10 mg/kg tetraabenazine s.c. One-half, 1, and 1- $\frac{1}{2}$ hours after tetraabenazine, the palpebral fissure, muscle tone of paws and nape, and spontaneous activity of the animals were noted. The administration of tetraabenazine alone produced a state characterized by hypotonia of paws and nape, lack of spontaneous activity, and closing of the palpebral fissure. The antitetraabenazine activity of the antidepressants amitriptyline, desmethylinipramine, and imipramine was described. The activity of promazine, chlorpromazine, dexedrine, nialamide, and iproniazid against tetraabenazine was also determined to test the specificity of the action produced by the antidepressants. The test was then applied to the screening of 13 dibenzocycloheptene derivatives for antidepressant action.

Department of Pharmacology
University of Brussels
Brussels, Belgium

2835 Stepanyan, Ye P., Bukharin, V. A., & Chernyavskaya, M. A. **Investigation of catecholamines in various organs of dogs under conditions of deep hypothermia.** Byulletin' Eksperimental'noy Biologii i Meditsiny, 9:56-60, 1963.

Catecholamine levels were measured in blood and various tissues of dogs (17 to 22 kg in weight) subjected to hypothermia (body temperature 10° C). Catecholamine levels in blood, adrenal glands, cerebral cortex, and heart were measured in anesthetized control dogs whose body temperature was kept at 37° C. In the experimental dogs, blood catecholamine levels were measured at several stages: just before anesthetization; just after anesthetization; at maximum cooling (10° C); 15 minutes after stopping the blood circulation; after reperfusion; before heating; and after heating. An unsuccessful attempt was made to measure skeletal muscle catecholamines. When the animals had been warmed to 37° C, catecholamine levels in the adrenals, heart, and cortex were determined. Catecholamine levels in the blood diminished sharply at maximum cooling and after the 15-minute stop in circulation. When the cooled blood was reperfused, levels increased slightly. When the blood reached normal temperature, levels increased 40% above control levels. Levels in the adrenals were 1 $\frac{1}{2}$ times higher than normal.

It was concluded that the decreased blood catecholamine levels during hypothermia lowered the tissue oxygen requirements.

Foreign Technology Division
Wright-Patterson Air Force Base, Ohio

336 von Euler, U. S., Ikkos, D., & Luft, R. **Adrenaline excretion during resting conditions and after insulin in adrenalectomized human subjects.** Acta endocrinologica, 38:441-448, 1961.

The effect of insulin on the urinary excretion of adrenaline was studied in 10 bilaterally adrenalectomized female patients, aged 47 to 73 years, receiving cortisone and in eight healthy volunteers. Insulin tolerance tests were performed in the morning in the postabsorptive state. Four units of insulin were given i.v., and the capillary blood glucose was determined before insulin and every 10 minutes thereafter for the first hour. Urine specimens for adrenaline analysis were collected for 2 to 2½ hours before and every hour for 3 hours following insulin. Blood glucose was determined by the method of Middleton and Griffiths (1957) and adrenaline by the method of Euler and Ishajko (1959). The resting excretion of adrenaline was the same in both groups. Insulin administration to the adrenalectomized patients led to an increase in adrenaline excretion from the control level (mean $\pm$ S.E.) of 2.42 ± 0.33 to 5.01 ± 0.98 ng per minute ($P < 0.02$) during the second hour, and 6.61 ± 0.82 ng per minute ($P < 0.001$) during the third hour. In the normal subjects the maximum adrenaline excretion (21.7 ± 3.49 ng per minute) was observed during the first hour. The response of the blood glucose level to insulin was the same in both groups. It is concluded that extra-adrenal chromaffin cells produce adrenaline and respond to insulin. It is suggested that hypoglycemia may not be the principal cause of this response.

Caroliniska Institutet
Stockholm, Sweden

337 Ritzel, G. & Hunzinger, W. A. **Über die Bestimmung von Katecholaminen im Urin. Normalwerte in Abhängigkeit vom Lebensalter und Befunde bei Hypertonie.** Determination of catecholamines in urine. (normal values and their relationship to age; findings in hypertension.)

Klinische Wochenschrift, 41(9):419-423, 1963.

Adrenaline, noradrenaline, and 5HIAA levels were determined in the urine of normal and of hypertensive patients of various age groups. A modified method for determination of the catecholamines is described; mathematical determination of the catecholamine values is discussed. The catecholamine content of 24-hour urine samples from 34 healthy adults was compared with that of 67 hypertensive patients of the same age. Values for the normal subjects are reported. Hypertensives showed an elevated excretion of noradrenaline. The age dependency of catecholamine excretion is described, based on 157 determinations in test subjects of various ages. Excretion of catecholamines increases with age, attaining a maximum between 50 and 70 years, then falling again. Pathologically elevated noradrenaline and 5HIAA excretion appears in infantile acrodynamia, and pathologically elevated adrenaline, noradrenaline, and 5HIAA excretion occurs in patients with pheochromocytoma.

University of Basle Medical Clinic
Basle, Switzerland

2838 Kassil', G. N., Matlina, E. A., & Sokolinskaya, R. A. **Adrenalin-like substances and biological activity of the blood in certain forms of nervous pathology.** Problemy Endokronologii i Gormonoterapii, 5(1):70-79, 1959.

The exchange of adrenaline together with the content of sympathins in the blood was investigated in order to determine the status of sympathetic and parasympathetic branches of the vegetative nervous system and to reveal the quantitative dependence between the level of adrenaline-like substances and the biological activity of the blood. Under investigation were the following groups of patients: 90 patients with diencephalic area afflictions, 64 patients with various pathological processes, 23 with myasthenia, 16 with myotonia, and 13 with Addison's disease. The clinical and biochemical data obtained from these patients were compared with that of 44 control subjects. The high level of adrenaline-like substances (adrenaline, dehydroform, and chromogens) and of sympathetic activity of the blood was noticed in cases of diseases accompanied with painful syndrome, in certain forms of diencephalic pathology, and in

Addison's disease. A low level of adrenaline-like substances of the blood was observed in myasthenia. An improvement in the patient's states was connected not only with changes in acetylcholine exchange, but also with the rise in level of adrenaline-like substances and with the increase of sympathetic activity of the blood.

(No address)

2839 Bruene, Guenter G., Hohl, Herbert H., & Himwich, Harold E. **Urinary excretion of bufotenin-like substance in psychotic patients.** *Journal of Neuro-psychiatry*, 5(1):14-17, 1963.

Paper chromatography was used in determining the presence of urinary indole amines resembling those of tryptamine, serotonin, and bufotenin-like substance in five schizophrenic and three mentally defective patients. Three schizophrenic patients and the mentally defective group were studied on various occasions during placebo administration. In addition, five schizophrenic patients received isocarboxazid (30 mg/daily) in combination with betaine (0.226 g/kg/day) in order to determine the effects of these agents on the urinary excretion of indole amines. In three of the five schizophrenics, a bufotenin-like substance was detected, but it was not found in the other two schizophrenic patients nor in the three mental defectives. During the placebo administration, indole amines resembling those of tryptamine and serotonin occurred in both groups of patients at all instances. In those receiving the MAO inhibitor with betaine, tryptamine and serotonin were detected in all instances, whereas the bufotenin-like substance was observed at various occasions in the same three patients who had excreted this compound during placebo administration. Spots resembling urea were found in all experiments.

Thudichum Psychiatric Research Laboratory
Galesburg State Research Hospital
Galesburg, Illinois

2840 Orikasa, Mutsuo. (Experimental studies on the effect of chlorpromazine on blood and organ lipids.) *Niigata Medical Journal*, 75:1020-1067, 1961.

The change in lipid levels in the blood and various organs of rabbits was measured after single and after repeated injections

of chlorpromazine, and was compared with changes in lipid level produced by reserpine, tetraethylammonium bromide, promethazine, and cortisone. A single injection of 5 mg/kg chlorpromazine caused a decrease in blood total lipid and total cholesterol level, but it caused only a mild decrease in phospholipid levels. When chlorpromazine (5 mg/kg) was given for 14 days, blood total lipid and total cholesterol levels increased but phospholipids decreased. Changes in these trends that occurred when rabbits were given high-fat, high-protein, or low-nutrition diets are recorded. With repeated injections of chlorpromazine (5 mg/kg daily for 14 days), under all types of diet, total lipid, total cholesterol, and total phospholipid levels increased in brain, adrenal gland, liver, spleen, kidney, testicle, heart muscle, skeletal muscles, and bone marrow. Tetraethylammonium bromide (20 mg/kg) and cortisone (5 mg/kg), like chlorpromazine, increased blood lipid, cholesterol, and phospholipid levels, but reserpine (0.2 mg/kg) and promethazine (5 mg/kg) caused a reduction in these levels. All the drugs increased lipid, cholesterol, and phospholipid levels in all organs except the adrenal gland and the bone marrow, in which, a decrease was observed.

Department of Internal Medicine
Fukushima Medical College
Fukushima, Japan

2841 Joanny, P. & Hillman, H. H. **Substrates and the potassium and sodium levels of guinea pig: Cerebral cortex slices in vitro: Effects of application of electrical pulses, of inhibitors and of anoxia.** *Journal of Neurochemistry*, 10:655-664, 1963.

The potassium and sodium of the non-inulin space of tissues maintained under conditions including lack of substrate, hypoxia or application of electrical pulses have been estimated in order to elucidate the mechanisms that maintain the ions at intracellular concentrations different from those of the media. Brain slices weighing 50 to 80 mg and 350 μ thick were taken from guinea pigs (300 to 400 g body weight). After 30 minutes of incubation in group I substrates, 10 mM glucose and 20 mM lactate, the maximum in vitro K and Na gradients were found (mean values, 102 to 108 μ equivalents/g and 70 to 74 μ equivalents respectively). Group II substrates, 10 mM L-glutamate and 10 mM glucose mixture, 20 mM pyruvate, 20 mM fructose, 10 mM L-glutamate (alone), and 20 mM oxaloacetate,

supported high non-inulin K and intermediate concentrations. Group III substrates, 10 mM succinate and 20 mM fumarate, gave non-inulin K of mean concentrations 7 μ equivalents/g only 10 μ equivalents/g higher than in the absence of substrate, and Na concentrations slightly higher at a mean of 130 to 132, which is 16 to 18 μ equivalents/g more than in the absence of substrate. Electrical stimulation (10 V, 100/second) for 10 minutes in the presence of all substrates tested, in the absence of substrate, and after 3 hours incubation without substrate caused a fall of K and rise of Na in the direction of their electrochemical gradients. About half the change was reversed during the 5 minutes after the end of stimulation, except in the absence of added substrates or with substrates of group III. In the absence of substrate for 3 hours followed by stimulation, or under anoxic conditions, the Na gradient was abolished, the K gradient diminished, tissue swelling doubled, and the tissue appeared damaged. Addition of 2,4-dinitrophenol (5×10^{-5} M) and sodium fluoride (5 mM) destroyed the Na gradient, but left a K gradient of 10 to 13. These decreases of ion gradients suggest that stimulation causes an increase in membrane permeability to both ions.

University of Aix-Marseille
Marseille, France

2842 von Euler, U. S. Occurrence and distribution of catecholamines in the fish brain. *Acta Physiologica Scandinavica*, 2:62-64, 1961.

Brains from hagfish (15 animals), dogfish (8 animals), and cod (5 animals) were examined for their content of catecholamines, and the brains of six specimens of dogfish were divided in seven portions (telencephalon, optic lobes, diencephalon, hypothalamus, hypophysis, cerebellum, and medulla oblongata) and examined for the distribution of catecholamines. Relatively high amounts of catecholamines were found in the brains of dogfish (adrenaline = 0.11 μ g/g of brain, noradrenaline = 0.37 μ g/g of brain, and cod (adrenaline = 0.03 μ g/g of brain, noradrenaline = 0.27 μ g/g of brain). Only small quantities could be found in the hagfish (adrenaline = <0.02 μ g/g of brain, noradrenaline = <0.02 μ g/g of brain). In the dogfish brain, the catecholamine amounts were highest in the diencephalon (adrenaline = 0.31 μ g/g, noradrenaline = 0.55 μ g/g), in the hypothalamus (adrenaline = 0.33 μ g/g, noradrenaline = 0.44 μ g/g), and in the hypophysis

(adrenaline = 0.41 μ g/g, noradrenaline = 1.5 μ g/g). These results indicate that catecholamines, as regulators of certain central nervous functions, enter relatively late in the evolution chain and that noradrenaline has a specific function in certain parts of the brain that may be the same in higher developed fish and mammals.

Karolinska Institutet
Stockholm, Sweden

2843 Remmer, H., Siegert, M., & Neuhaus, G. Die Elimination von Glutethimid und von langwirkenden Barbituraten nach toxisch und therapeutisch wirksamen Dosen. (The elimination of glutethimide and of long-acting barbiturates after toxically and therapeutically effective doses.) *Naunyn-Schmiedeberg's Archiv für Experimentelle Pathologie und Pharmakologie*, 245:471-483, 1963.

Because of the danger of chronic intoxication due to the accumulation of hypnotics in the organism, studies were made on the elimination of several hypnotics in human and animal subjects. Glutethimide in the blood was determined by the improved method of Goldbaum. Blood barbital and phenobarbital were determined by methods developed by the authors. The results showed the following: (1) In subject patients, 80% to 90% of p.o. therapeutic doses of glutethimide was eliminated within 24 hours. (2) The rate of elimination of phenobarbital in one of two cases of attempted suicide began to show an exponential drop after 6 days. (3) In experiments using dogs, elimination was protracted after administration of large doses of phenobarbital (30 to 60 mg/kg) p.o., but not after i.v. injection. Phenobarbital elimination increased greatly after the third or fourth day. However, barbital concentration in the organism dropped exponentially after either p.o. or i.v. administration. (4) Upon repeated administration of glutethimide to 15 Sprague-Dawley rats, the duration of the drug and narcotic effect decreased, with males showing a more rapid decrease than females. The action of hexobarbital is similarly shortened after pretreatment with glutethimide. (5) The rate of elimination of total 4-aminoantipyrine in three patients that had been given 1-g injections of noramidopyrine methanesulfonate sodium. This is accelerated by 80% to 90% with p.o.

administration of 15 g glutethimide, and heightened elimination of the oxidation product is observed for a 3-week period.

Pharmacological Institute
Free University of Berlin
Germany, Berlin

2844 Koechlin, Bernard A. & d'Arconte, Lucius. **Determination of chlordiazepoxide (Librium) and of a metabolite of lactam character in plasma of humans, dogs, and rats by specific spectrofluorometric micro method.** Analytical Biochemistry, 5:195-207, 1963.

The chemical structure and characteristics of chlordiazepoxide are discussed. A sensitive and selective spectrofluorometric method was developed for the determination of chlordiazepoxide and, with slight modification, lactam (metabolite) in blood plasma. It is based on the conversion of chlordiazepoxide to the lactam under controlled hydrolytic conditions followed by rearrangement of the *N*-oxide grouping in alkaline solution under the influence of light to a fluorescent derivative. With a sensitivity limit of 0.25 γ /ml of plasma for either compound, the method was adequate for measuring plasma levels of chlordiazepoxide as encountered after normal therapeutic doses in humans (10 to 30 mg). Plasma levels of chlordiazepoxide, after a single injection of 30 mg or in divided doses, were determined in human subjects. The maximum levels of 1 to 2 γ /ml occurred 2 to 4 hours after administration but were maintained longer after the divided doses. Dogs were given 4 and 10 mg of chlordiazepoxide, the maximum plasma concentrations being 6 to 12 γ /ml. The lactam plasma levels after 10 mg/kg were similar to those of chlordiazepoxide. Ten rats were given 15 mg/kg of chlordiazepoxide, and the maximum plasma levels of 8 to 10 γ /ml occurred in 2 hours. The half-lives of chlordiazepoxide were 20 to 24 hours in humans, 14 to 20 hours in dogs, and 4 to 6 hours in rats.

Department of Pharmacology
Hoffman-La Roche Incorporated
Nutley, New Jersey

See also: 2662, 2673, 2685, 2693, 2722, 2736, 2781, 2782, 2785, 2796, 2798, 2805, 2811

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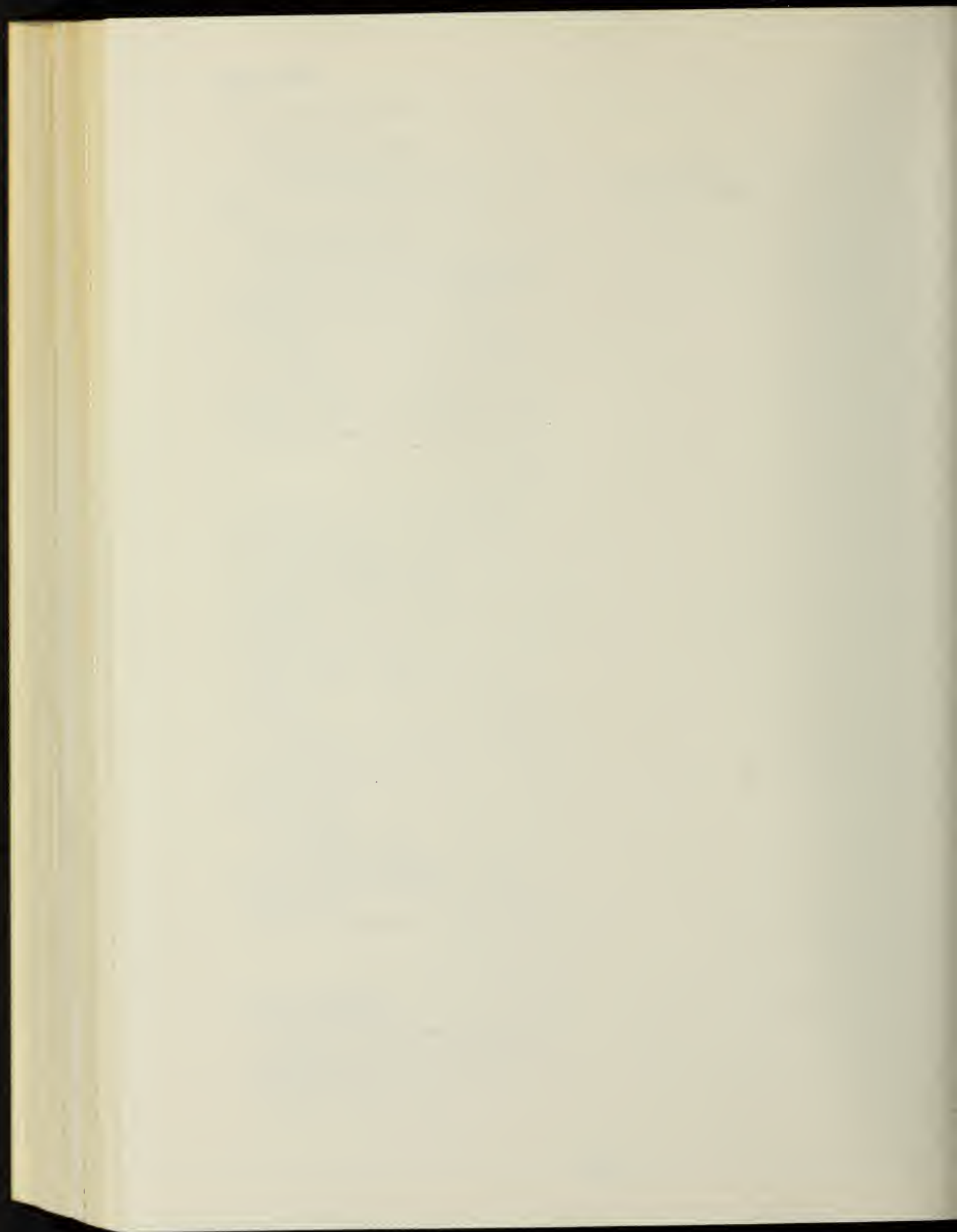
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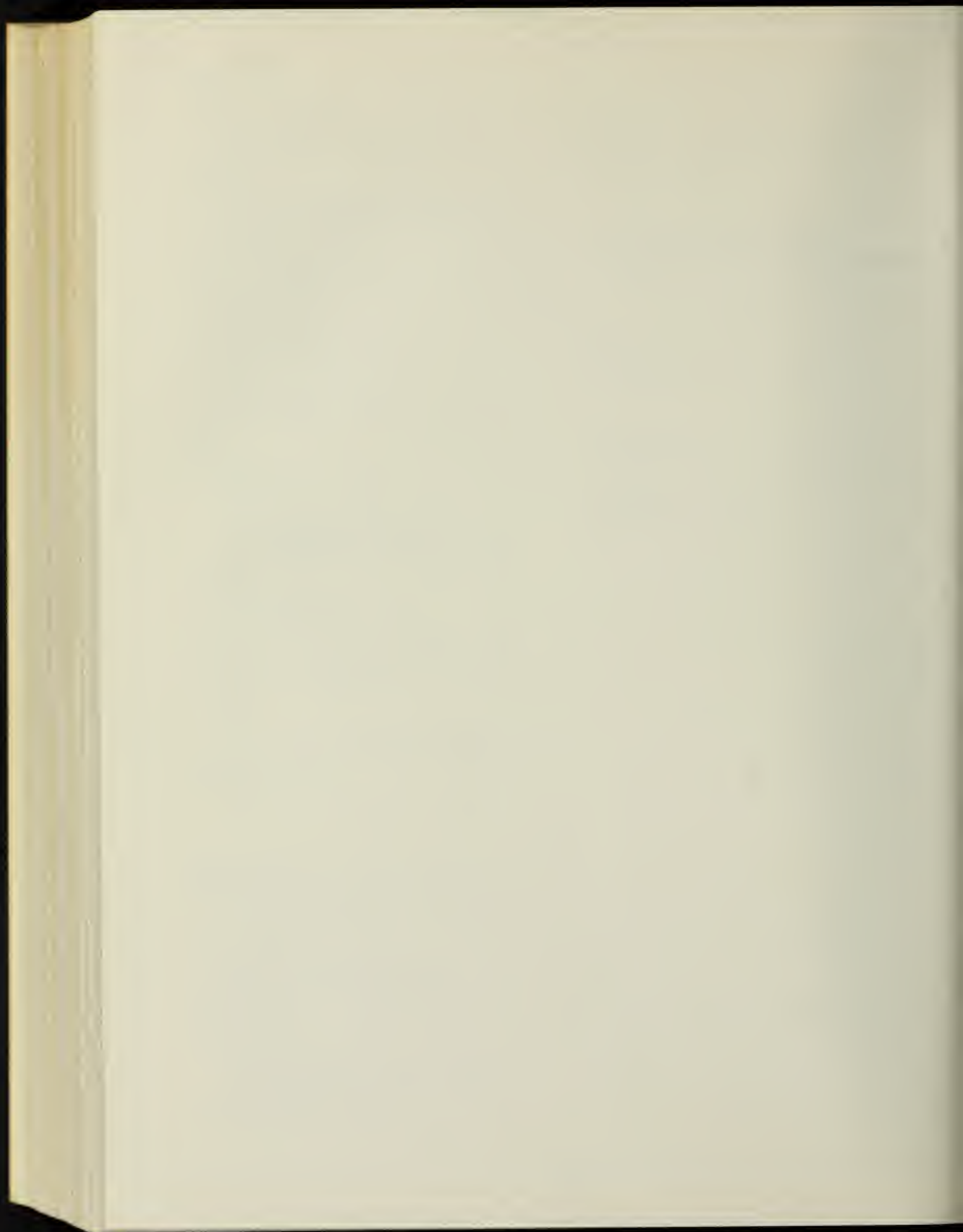
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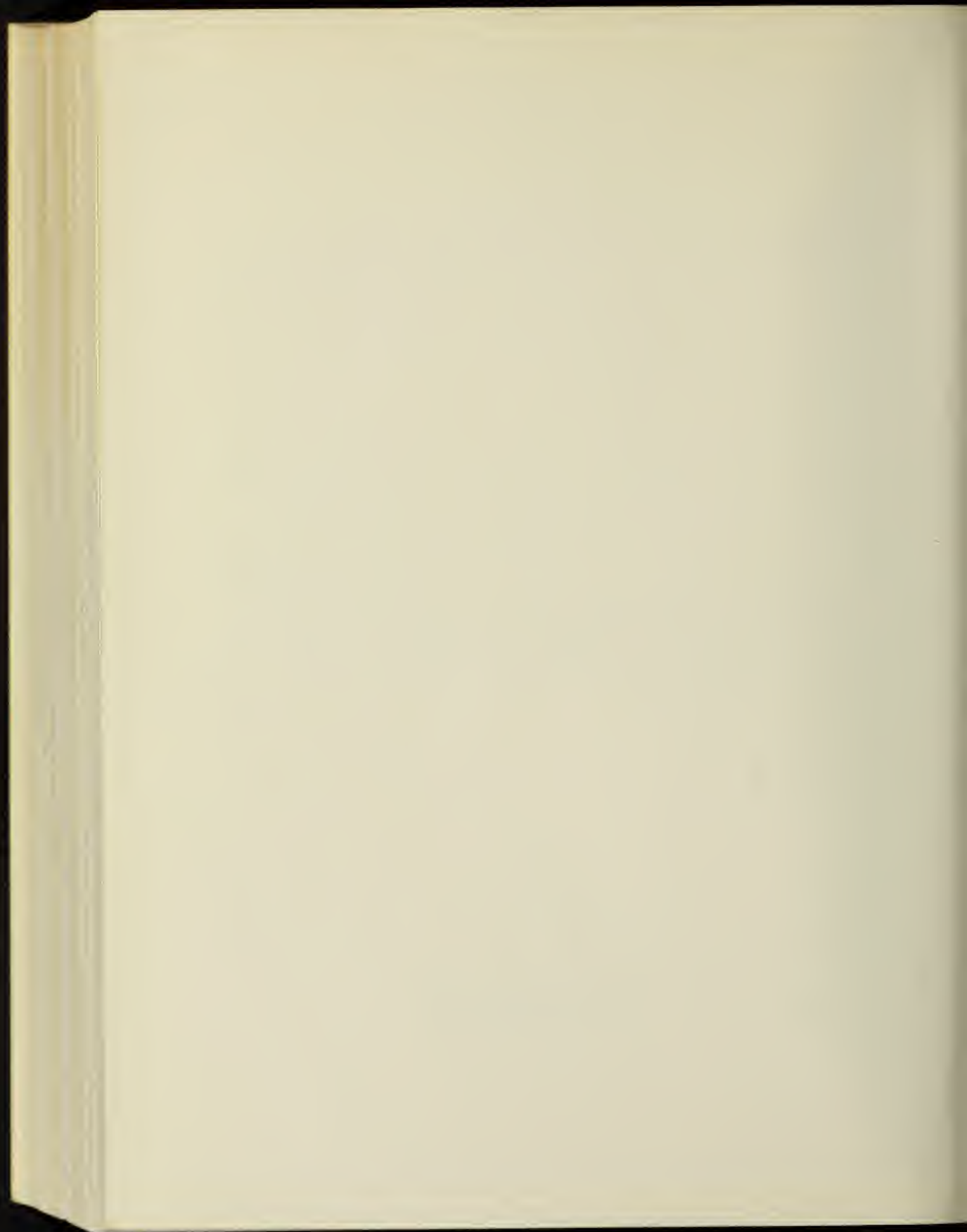
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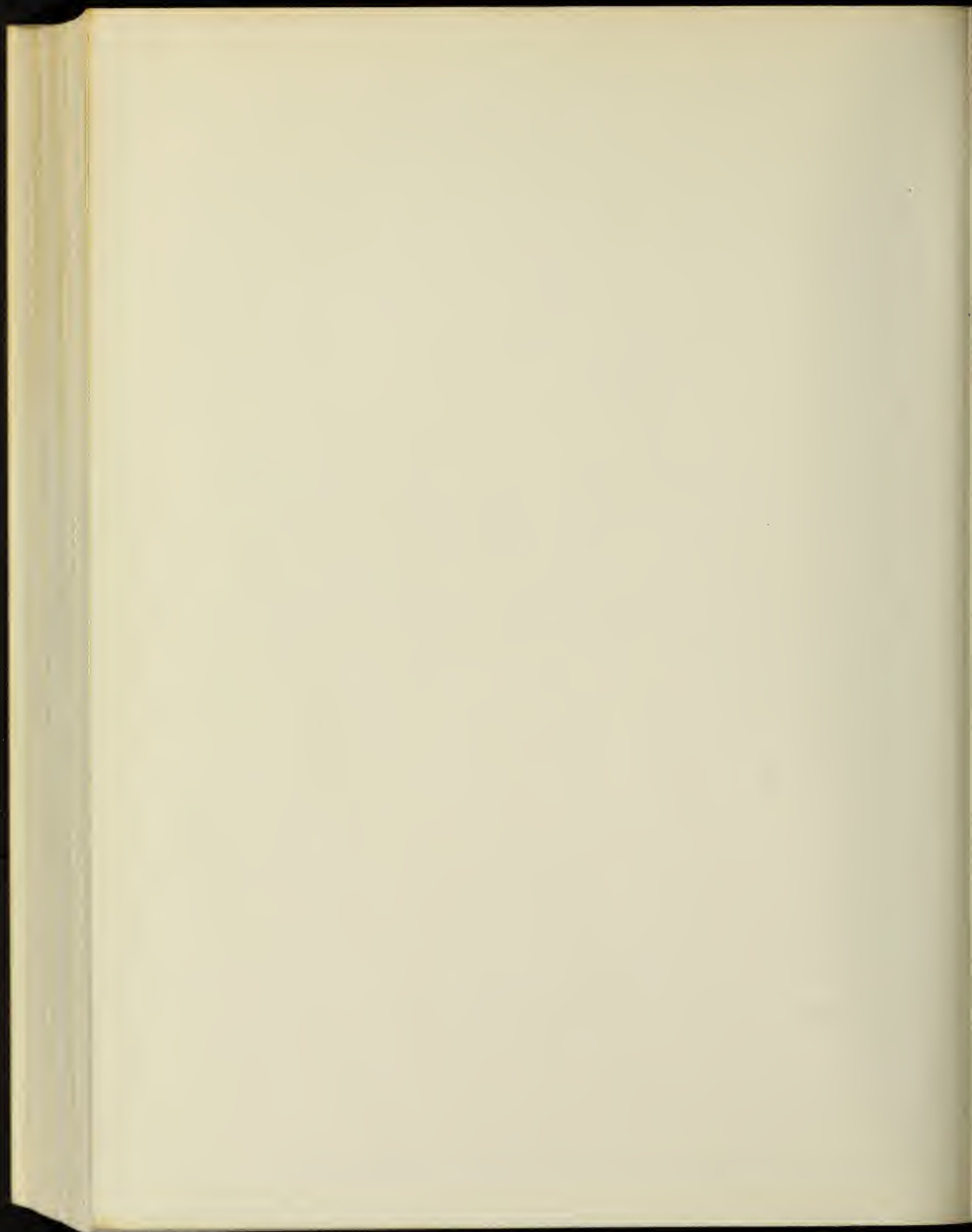
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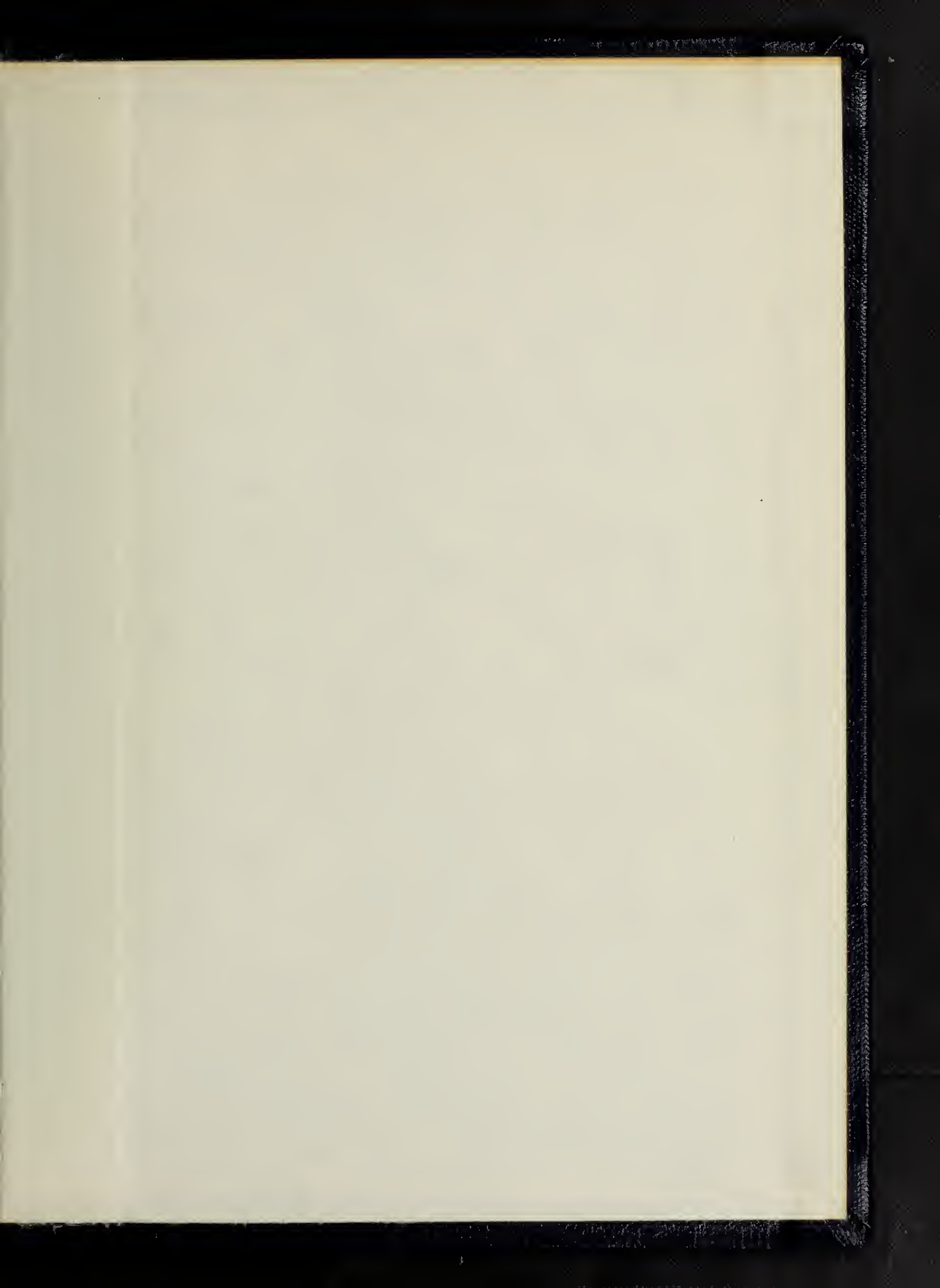
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